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# HEART.

## A JOURNAL FOR THE STUDY OF THE CIRCULATION.

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## THE REGULARITY OF SIMPLE PAROXYSMAL TACHYCARDIA.\*

By H. S. FEIL, Cleveland, and M. D. D. GILDER, Bombay.

(*University College Hospital Medical School.*)

RECENTLY, in an article to this Journal, Lewis published a series of accurate comparator measurements of the intervals between cycles in clinical auricular flutter, pointing out that a high degree of regularity exists. He showed that the variations in the lengths of the inter-auricular intervals averaged less than 0.0009-0.0077 of a second in curves, including 17 to 32 cycles. The maximal variations in the same curves were usually less than 0.01 of a second.

It was suggested that similar measurements should be made on electrocardiograms from eight cases of paroxysmal tachycardia in the same collection of curves, from 11 to 18 cycles being measured on each record. As was done in the measurement of the flutter cycles, the inter-ventricular intervals were measured because of the greater accuracy in reading the ventricular peaks, and because in several instances the actual auricular complexes were obscure or invisible. The intervals showed a conspicuous degree of regularity, which appeared to be independent both of the rate of the individual tachycardias and of their points of origin. In these eight cases the maximal differences in the inter-ventricular intervals varied from 0.0071 to 0.0358 of a second and were usually below 0.0099 of a second. The average variations in the lengths of the intervals ranged from 0.0010 to 0.0092 of a second, but were usually below 0.0022 of a second. In those cases, which were frankly auricular in origin, the actual degree of regularity of the auricle was possibly greater, since the measurements included any variations in the *As-Vs* conduction period which may have been present.

Thus, in comparing paroxysmal tachycardia with auricular flutter, we find a similar degree of regularity, as is shown in Table II, in which the corresponding variations are tabulated.

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\* Carried out on behalf of the Medical Research Council.

TABLE I.

*Length of ventricular cycles in paroxysmal tachycardia.*

Patient.	Date.	Site of impulse formation.	Duration.	Rate per minute.	Max. diff. in secs.				Average length in secs.	Average variation in secs.				
B. 10	12/11/11	Auricular	Long contin'd	157	3806	3822	3843	3817	3806	3844	3825	3806	3807	-00017
					3802	3800	3845	3824	3822	3827	<b>3785</b>	3826	3807	
T. 172	3/11/11	Auricular (low)	Short	144	4253	<b>4265</b>	4242	<b>4031</b>	4145	4210	4252	4226	4132	-00058
					4207	4188								
R. 742	21/6/12	Probably auriculo-ventricular alternation present	Long	214	2836	2810	2833	2770	2813	2808	2838	2798	2848	-00022
					2828	2801	2788	2770	2813	<b>2851</b>	<b>2752</b>			
L. 1531	4/2/13	Ventricular (probably)	Long contin'd	185	3226	3225	3227	3212	3270	<b>3212</b>	3215	3274	3242	-00021
					3250	3237	3219	<b>3305</b>	3251					
P. 1601	19/2/13	A. V node	Long contin'd	203	<b>2894</b>	2933	2897	2975	2951	2952	2974	2967	<b>2984</b>	-00021
					2974	2950	2961							
S. 1810	16/5/13	Auricular A. V block also present	Short	129	4655	4647	4642	4646	4654	4630	4661	<b>4694</b>	4659	-00010
					4647	4647	<b>4623</b>	4657	4652					
G. 1843	19/5/13	Probably A. V node		185	3161	3278	3132	3345	3126	<b>3434</b>	<b>3076</b>	3293	3273	-00092
					3328	3242	3311	3138	3313	3095	3331			
F. 1882	27/5/13	Probably A. V node	Long contin'd	170	<b>3566</b>	3516	3506	<b>3477</b>	3511	3509	3558	3523	3512	-00018

TABLE II.

	<i>Auricular flutter.</i>	<i>Paroxysmal tachycardia.</i>
Maximal differences in seconds	0.0037-0.0265, usually less than 0.01 of a second.	0.0071-0.0358, usually less than 0.01 of a second.
Average variations in seconds.	0.0009-0.0077, always average less than 0.01 of a second.	0.0010-0.0092, always average less than 0.01 of a second.

## SUMMARY.

A high degree of regularity was found in the cycles of curves from eight cases of paroxysmal tachycardia; the degree of regularity approached that seen in clinical auricular flutter. The maximal differences in the lengths of ventricular cycles varied from 0.0071 to 0.0358 of a second in different cases, and were usually below 0.0099 of a second. Thus, the maximal differences rarely exceeded 0.01 of a second, and the average variation never reached 0.01 of a second.

# THE PULSE IN AORTIC DISEASE AS FELT AND GRAPHICALLY INSCRIBED.\*

By H. S. FEIL, Cleveland, and M. D. D. GILDER, Bombay.

(*University College Hospital Medical School.*)

THE primary object of the present observations is a comparison of the sensations experienced in palpating the radial pulse in cases of aortic disease with curves obtained from the same pulse, accurately inscribed on a travelling surface, thus exploring the extent to which the several characters of the pulse encountered in this valvular lesion may be identified by simple clinical means. For very many years the pulse in aortic disease has been known to convey definite impressions to clinicians, and the various types have been classified as (1) water-hammer, (2) double-topped (*bisferiens*), (3) anacrotic, and (4) flat-topped. Corrigan,<sup>1</sup> in his admirable clinical description of cases of aortic disease, said: "But when the valves, becoming inadequate to their office, permit some of the blood contained in the ascending aorta, carotids and subclavians, to return into the left ventricle after each contraction, then the aorta and these trunks become . . . partially flaccid; and at the next contraction of the ventricles the blood propelled into them is sent along as a rushing current, which throws the sides of these arteries into vibrations, and these vibrations give to the ear *bruit de soufflet* and to the finger *frémissement*. The *frémissement*, or rushing thrill, described as easily felt in the subclavians and carotids, can sometimes be felt by moderate tact as far as the pulse in the wrist." Later, Corrigan spoke of the increase of arterial pulsation by elevation of the arms, due, as he said, to the relative emptying of the arteries.

Since Corrigan's time much work has been done in comparing the sensation with the inscribed records, but largely before accurate methods were devised. The instruments commonly used, the Dudgeon and Marey sphygmographs, introduced considerable errors, chiefly of the following nature: (1) Eventual over-riding in response to quick changes of pressure, sometimes so considerable as to introduce wholly artificial summits or dips. (2) Inability of the instrument to follow very quick changes in pressure, and the consequent damping out of minor oscillations in the curves.

\* Observations undertaken on behalf of the Medical Research Council. The direction and aid of Dr. Thomas Lewis, in whose laboratory the work was done, is gratefully acknowledged.

(3) Distortion of the curves brought about by the inertia of the lever system; by looseness of joints of the lever system; and by the actual inscriber writing in the arc of a circle rather than in a vertical line.

These errors of technique have been largely, if not entirely, abolished by optical recorders, of which Frank's capsule is a notable example.

The apparatus used in our observations consisted of a Frank segment capsule mounted on an adjustable stand and connected with the Wiggers type of radial transmission sphygmograph by thick walled rubber tubing. The optical arrangement was similar to that described by Wiggers,<sup>2</sup> but modified in the arrangement of the time-marker. A second beam of light, from the same source as that illuminating the capsule—but broader—was reflected from a vertical plane mirror upon the photographic plate. This light was cut at its source by a rotary tuning fork time-marker and thus the plate was fogged intermittently. The lines thus ruled are sharp, cross the entire record, and enable us accurately to measure the curves. The recording apparatus was the plate camera used in electrocardiography (made by the Cambridge and Paul Instrument Company).

In testing the oscillation frequency of the recording mirror, a record of the oscillations resulting from sudden release of pressure in the air system of the recording apparatus was taken. The record shows a sudden dip when the pressure in the air system falls—followed by a number of small waves; the rates of these oscillations have varied from 46 to 79 per second during the course of the experiments. These small waves express the frequency of the membrane and mirror. This frequency makes it possible to record—undamped—oscillations occurring in the vessel at these rates or below them.

The radial pulse has been investigated exclusively because of the purpose of this research, namely, a comparison of the clinical examination of the pulse with the graphic record. All curves were taken with the patient in the dorsal position, with the arm held horizontally or vertically. The latter position was used because of the well-known fact that the water-hammer quality is best appreciated with the arm held vertically, and also in order to investigate the sensation of thrill which is sometimes felt at the pulse in cases of free regurgitation, especially when the arm is raised. The systolic and diastolic pressures (auscultatory) in the brachial artery were taken at the same time, with the patient in the dorsal position. All measurements of the plates were made on the Lucas comparator.

The points on the curves which were selected for measurement were: (1) The beginning of the upstroke; (2) a point on the upstroke at one-half its total height; (3) the peak of the primary wave; and (4) the peak of the predicrotic wave, or other secondary wave occurring about this time, if either of these were present. The intervals were converted into seconds by the method recently published by Lewis.<sup>3</sup> From these measurements the following intervals were ascertained:—(1) The interval between the beginning of the upstroke and a point halfway to the first summit: (2) the

interval between the beginning of the upstroke and the top of the first summit (primary wave): (3) the interval between the beginning of the upstroke and the summit of the predicrotic wave: and (4) the interval between the primary summit and the predicrotic summit or its equivalent.

The reason for calculating the first of these intervals is as follows:—In normal curves the rise of the primary wave to its actual summit occupies a time which is somewhat more than double that taken for the primary wave to rise to half this level. In comparing the rate of rise for various normal curves the half-way measurement presents little advantage. But when, as in many cases of aortic disease, the initial rise is steeper, the primary wave is often continued in the form of a rounded plateau (see Fig. 2). In such cases the first half of the rise to the actual summit occurs in a time interval, which is but a small fraction of the time interval taken for the whole rise: it is this quick initial rise which is often responsible for the chief impression conveyed to the palpating finger.

The measurements alluded to (1 to 4) have been tabulated side by side with descriptions of the sensations conveyed by the pulse to the palpating finger. These clinical notes were written down in each instance before the records were taken, so that the comparisons might remain unprejudiced.

The clinical notes have been kept in a relatively simple form, because it was thought that the tabulated comparisons between the clinical examinations and the measurements of the inscribed curves would convey the results of the observations more accurately if the pulse was described in general terms.

The description of the pulse is, in many instances, incomplete, for the reason that, as the work proceeded and individual comparisons were made, the clinical descriptions tended to become more elaborate.

For the purposes of this research we studied 10 normal cases and 33 cases of aortic disease. The normal individuals were medical students and laboratory workers of healthy aspect, free from any abnormal physical signs in the circulatory system and varying in age from 15 to 38 years. The aortic cases were taken from Dr. Lewis's clinic, and all but one were ex-service men.

Three or more pulse beats were measured and the average of these measurements used. Several of the curves were measured more than once, and where the peaks were well defined the measurements were within the errors of observation as stated by Lewis.<sup>3</sup>

#### *The normal radial pulse curve.*

The records of the normal adults were taken and measured in such a way that the figures might be compared with those of the aortic cases. The normal curves showed the three usual chief waves: (1) the primary wave, which constitutes the summit of the pulse (the rise to the summit is gradual and occurs in from 0.075 to 0.130 of a second); (2) a small blunt



peak on the decline of the first wave, namely, the predierotic wave, which appears 0.112 to 0.180 of a second later; and, finally, (3) the dierotic wave. The half-way point on the upstroke of the primary wave occurs from 0.031-0.051 of a second after its onset; usually the figure is 0.038 to 0.047 of a second. Table I compares the measurements of the records of normal pulses taken with the arm horizontal and with the arm vertical. The tabulation shows little or no change in the time of the appearance of the primary wave, the predierotic wave, and the point half-way to the summit of the primary wave.

*The pulse in aortic disease.*

For descriptive purposes the pulses of aortic disease have been grouped into six classes according to their types.

Class I (Table II, Fig. 2) includes conspicuous water-hammer pulses in which a thrill is palpable when the arm is held in the vertical position. In the records the upstroke is large and abrupt: it passes into a rounded summit or plateau which is succeeded by a steep fall to the dierotic notch, and a series of oscillations, usually three to six in number, are found on the upstroke or on the summit. The half-way point on the upstroke occurs at 0.006-0.018 of a second after the beginning of the rise, and the highest point of the summit occurs at 0.031-0.100 of a second. The oscillations, which graphically represent the palpable thrill, individually have an average duration of 0.02 of a second, *i.e.*, the vibration frequency for the thrill is approximately 50 per second.

Class II (Table III, Fig. 3) comprises water-hammer pulses of rather less conspicuous type. The graphic records are again characterised by a relatively sharp and large rise: the primary summit is a single peak: an ill-defined second peak occurs on the downstroke, and the pulse falls away most quickly directly before the dierotic notch. The half-way point is found 0.024-0.030 of a second after the beginning of the elevation, and the primary summit is reached in from 0.064 to 0.081 of a second.

In Class III (Table IV, Fig. 4) are aortic pulses giving to the observer the impression of a water-hammer with an indistinct or doubtful bisferiens quality. The records are characterised by a relatively sharp rise, by the presence of two conspicuous summits, the first being of greater height, and separated from the second by from 0.142 to 0.156 of a second, and by a distinct vibration or hesitation on the upstroke. The chief fall of the pulse wave precedes the dierotic notch. The half-way point occurs 0.018-0.040 of a second, and the primary summit 0.070-0.107 of a second, after the beginning of the upstroke. This group merges with that next described (Class IV).

In Class IV (Table V, Fig. 5) are included the records from cases of aortic disease showing unmistakable pulsus bisferiens. The rise of the pulse wave in the majority of the cases gives the examiner the impression of abnormal quickness, and in all cases but one of the present series, the

double top was clearly detected clinically. In four instances a suggestion of thrill was felt when the arm was held vertically. The curves are characterised by the relatively sharp and big rise and by the two very conspicuous summits of nearly equal height. The second peak falls sometimes a little short of the first in amplitude and is separated from the first peak by 0.106\* to 0.182 of a second. On the main upstroke a distinct vibration or hesitation is seen in some of the curves, especially with the arm in the vertical position. The chief drop of the pulse wave precedes the dirotic notch. The half way point occurs from 0.017 to 0.044 of a second, the primary summit from 0.060 to 0.105 of a second after the upstroke; the second peak follows the first after from 0.106 to 0.182 of a second. It has been observed that some pulses which are bisferiens in the horizontal position become anacrotic when the arm is raised to the vertical.

Class V (Table VI, Fig. 6) merges into the bisferiens group, and includes the records of anacrotic pulses. The curves show smaller pulses than those in the last group—some conspicuously so. The graphic pulse wave has two more or less prominent summits, the second somewhat higher, or distinctly higher, than the first. At times the first summit is less distinct and then tends to hold an even lower level relative to the summit of the pulse. Exceptionally the initial rise is rapid, and it may then present a distinct vibration. The primary (anacrotic) wave appears 0.055 to 0.100 of a second after the beginning of the first rise, and the highest peak occurs 0.122 to 0.171 of a second later than the anacrotic. This group merges imperceptibly into the last and sixth class.

Class VI (Table VII) comprises a few curves showing a single blunt peak with a relatively slow rise. The half-way point comes from 0.043 to 0.053 of a second, and the peak from 0.110 to 0.131 of a second, after the beginning of the upstroke.

*Water-hammer quality.* This characteristic of the pulse, long recognised as the most distinctive of aortic regurgitation, is due to initial steepness of the primary upstroke. In all instances in which the pulse is of considerable amplitude, and in which the rise occurs with conspicuous abruptness in the measured records, as in Class I (Table II), this quality is recognised clinically and is described as "water-hammer," the term being usually qualified by the adjective conspicuous. The normal pulse rises to the half-way point in 0.031 to 0.051 of a second with the arm horizontal, and in 0.039 to 0.051 of a second with the arm vertical. In cases of aortic disease with conspicuous water-hammer pulse the pulse rises to the half-way mark in from 0.006 to 0.018 of a second, the arm being held vertically; the rise to the half way point of pulses of conspicuous or less conspicuous water-hammer quality occurs in 0.018 to 0.040 of a second with the arm horizontal,

\* The first figure, 0.106 of a second, is exceptional, and in this instance there was uncertainty as to whether the two distinct peaks could be felt clinically.

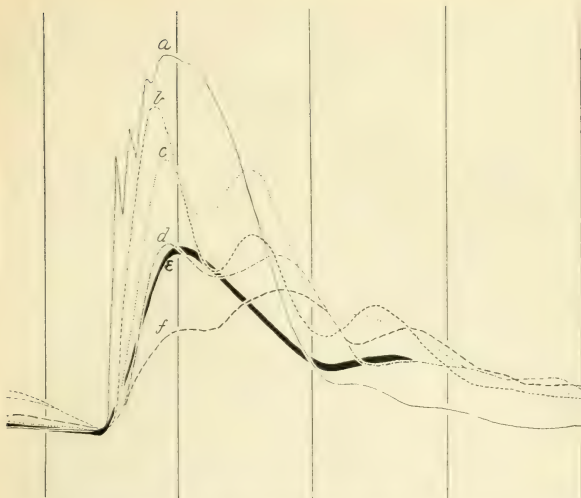


Fig. 1. Curves illustrating the chief types of pulse in cases of aortic disease and a normal pulse curve. The normal pulse record is drawn with a heavy line. The vertical lines represent time in fifths of a second.

- (a) Class I: Abrupt up-stroke and thrill.
- (b) Class III: Relatively abrupt up-stroke with two peaks, the second appreciably smaller.
- (c) (d) Class IV: Less abrupt up-stroke with two equal peaks (bisferiens).
- (e) Normal record.
- (f) Class V: Anacrotic pulse.

and in 0.006 to 0.030 of a second with the arm vertical. The upstroke of the water-hammer records is evidently much more abrupt than in the normal pulses.

The intervals cited do not fully represent the quickness of the rise of the pulse wave in aortic disease, because they take no account of the exaggerated pulse pressures. As this factor cannot be measured accurately it is omitted. That the pulse assumes the water-hammer quality most conspicuously when the arm is held vertically is confirmed by the fact that the measured rise in instances of water-hammer pulse is found to be notably decreased in duration when the arm is elevated. The increase of speed of the up-stroke varies from 50 to 400 per cent.; it is usually about 100 per cent.,

Table VIII contrasts the measurements of records of aortic cases taken horizontally with those taken vertically. Corrigan<sup>1</sup> noted the conspicuous increase in arterial pulsation with elevation of the extremities, stating that a patient first pointed out this circumstance to him, and related that raising his arms above his head greatly increased the pulsation of the vessels of the arm and hand.

*Quality of thrill.* Corrigan called attention to the phenomenon of thrill (*frémissement*) to be felt in "subclavian and carotids . . . by moderate tact as far as the pulse in the wrist." He noted also that the *frémissement* was most obvious with elevation of the arms. He suggested that the physical sign is due to the vibration of the arterial walls by the blood current in the relatively empty vessels. This palpable thrill or pseudo-thrill is known to clinicians, and in our experience also is much more palpable when the arm is held vertically than horizontally. In some few cases it is unmistakable, and in some instances it is elusive owing to its brief duration. It consorts almost if not exclusively with pulses in which the upstroke is of extremely brief duration.

In all the records of Class I (Fig. 2), which were taken without exception from arms held in the vertical position, this thrill is manifest. Individual oscillations have an average duration of 0.02 of a second; that is to say, a frequency of 50 per second. The thrill was noted by palpation in three of these five cases.

Of instances in which a thrill or a tendency to thrill was noted clinically, three examples fall where they belong, namely, in Class I, which comprises pulses from which the thrill was clearly recorded graphically. In two instances of the same group a thrill was inscribed that was not noted clinically. On the other hand, a tendency to thrill was spoken of clinically in one case, but no trace of thrill was recorded graphically; in this case an abrupt upstroke was present, however. The incomplete harmony between the clinical notes and the records in respect to thrill is in part, if not entirely, explained by differences in external pressure. When records are taken from the same pulse, with different pressures of the wrist band, the conditions otherwise being similar, the oscillations which constitute the thrill may be seen in some records and not in others. It is also true that the pressure exerted by the palpating fingers requires nice regulation before the thrill becomes apparent (as noted by Corrigan).

*Collapsing quality.* We believe that the apparent quality of collapse in the aortic pulse is largely more imagined than real. That the fall of pressure from the systolic to the diastolic level is greater in aortic regurgitation (the systolic pressure being high, and the diastolic pressure low) than when normal pressures prevail is quite clear; but that there is a particular phase of the pulse cycle during which the pressure falls with remarkable steepness does not appear to be borne out by the

majority of records. It is probable that what is termed the quality of collapse is often or usually caused simply by the cessation of the abrupt upstroke. Sometimes there is an initial and comparatively steep fall immediately at the end of the upstroke, but this fall is never very pronounced in extent. The chief fall takes place from the summit of the main peak to the bottom of the dicrotic notch, and rather in the late than early phases of this period. Relatively, the fall of the curve from the dicrotic onwards does not seem to be more conspicuous than that seen in normal curves. The lines of most rapid descent in the arterial wave are accomplished before regurgitation begins. It seems clear to us that the chief qualities of the aortic pulse are due rather to the low diastolic pressure prevailing when systole starts and to the character of this systole at its onset and during its progress, than to the actual regurgitation through the aortic valves.

*Bisferiens quality.* In grouping the graphic records we have placed together (Class IV, Table V) the curves showing two prominent summits of nearly equal amplitude. The curves in which two prominent summits appear, but in which the second is of distinctly less amplitude than the first, have been grouped separately (Class III, Table IV), though some of these may be termed bisferiens clinically. The bisferiens quality of the aortic pulse is usually quite distinct to the touch: two summits are appreciated, the second following very quickly on the first. In palpating pulses the second peak, although present, is not generally felt as an unmistakable phenomenon, unless it rises to the level approximately of the first summit, although there are exceptions to this rule. Of more frequent occurrence are the instances in which the pulse is termed bisferiens clinically, but where the records show the second summit somewhat higher than the first, a pulse belonging properly to the anacrotic group.

The interval separating the two peaks is a factor of obvious consequence in determining the palpability of the twin summits. Given two summits, these can be identified clinically with ease at their usual interval, 0.146 to 0.182 of a second.\* One record, showing two peaks separated by an interval of 0.130 of a second, was taken from a pulse described as "large, sharp upstroke, thrill." In another curve of this same group the peaks were separated by 0.106 of a second, and the clinical description was "quick rise; large pulse; suspicion of double top and thrill."

*Anacrotic quality.* The term anacrotic pulse is generally used clinically, we think, to express a relatively slow rising pulse, irrespective of the presence of two palpable summits. If the term is to be accurately applied clinically it should be limited to pulses in which not only are the two summits distinctly palpable but in which the second is recognised as

\* The normal interval between primary and predicrotic summit lies between 0.130 and 0.180 of a second.

being distinctly higher than the first. It must be evident that where the difference in the amplitude of the two summits is slight the second distinction cannot be accomplished; neither it is of great clinical import. Unquestionably the slow rise is the outstanding clinical feature of the pulse which gives anacrotic records. This impression of slow rise is acquired from the duration of the interval between the beginning of the upstroke and the summit of the pulse wave as a whole, for this summit in the anacrotic pulse is not the primary peak but the second; to the finger the latter, which is the actual summit of the pulse, is most prominent. The interval between the upstroke and the first summit of the anacrotic pulse is no greater than the corresponding period of the normal curve (*i.e.*, between the upstroke and the actual pulse summit), and lies usually between 0.078 and 0.100 of a second. Inasmuch as the anacrotic pulse is of small volume and the excursion to the summit of the first peak is a reduced excursion, it may be said that the initial rise of pressure is slow, although the rise is accomplished in normal time. Nevertheless, this does not appear to be sufficient to explain the impression of the extremely slow rise which is conveyed to the palpating finger. We ascribe this mainly to the fact that the pulse continues to ascend to the summit of the second peak. The measurement of the upstroke to the summit of the second peak (the summit of the pulse) is about 100 per cent. greater than the interval between the upstroke and the summit of the normal pulse. Change of position of the arm has little or no effect on the measurements of the records in the anacrotic group.

Where the graphic record shows the second peak very distinctly greater in amplitude than the first peak, the pulse is almost always described clinically as anacrotic. Where the difference in the amplitude of the two peaks is trifling the clinical impression may be that of an anacrotic or of a bisferiens pulse, the first diagnosis predominating when the pulse excursion is small, the second when the excursion is greater. In a few instances it is possible to appreciate with the finger not only the slow rise of the pulse to its summit and the presence of two peaks, but also to be fairly certain that the second peak is greater in amplitude than the first.

*Pulses combining the water-hammer and the anacrotic quality.* Some few pulse curves in aortic cases combine the qualities of water-hammer and anacrotic records; there may be in the early phases of the upstroke an abnormally abrupt rise of pressure, yet the first peak may not actually be the summit of the pulse. One type of this combination is seen in the curves of Fig. 2, Class I, where the extremely abrupt upstroke is followed by a line which still ascends. This type and the record in which there is a single small oscillation near the centre of a relatively abrupt upstroke (Class III, Fig. 4) are perhaps not correctly termed anacrotic, in that this term usually applies that the first or lower peak corresponds to the primary wave of a normal pulse. There are, however, occasional instances where the

recorded pulse is of the true anacrotic type but where the first portion of the upstroke is abnormally steep (an example is shown in Fig. 6. c.). Such pulses may or may not be identified as anacrotic clinically.

In a number of instances pulses may be termed anacrotic clinically, while in the graphic records the first summit is scarcely to be distinguished. There is a gradual transition from the anacrotic records, on the one hand, to those in which the pulse wave rises after a great delay to a single summit. Unless the two summits of the true anacrotic types are very clearly defined on the records, the two peaks cannot be appreciated by palpation.

#### SUMMARY.

The pulse as recorded graphically in aortic disease is exceedingly varied in form: the chief abnormal qualities which it presents, and these may be displayed singly or in combination, are:—(1) Unusually abrupt upstroke: (2) the presence of two prominent summits which may be of equal or almost equal height (*bisferiens*) or of which the first may be of distinctly less amplitude than the second (*anacrotic*): and (3) the occasional presence of rapid oscillations on the upstroke or plateau, constituting a brief thrill. All of these qualities may be recognised to a greater or less extent by the palpating finger.

The impression of the water-hammer quality is caused by the abruptness with which the pulse pressure rises and by this alone. The impression of the slow rise when the pulse is anacrotic is brought about by the great increase in the interval between the beginning of the upstroke and the actual summit (*i.e.*, formed in this instance by the second peak). The *bisferiens* quality is distinctly palpable when the summits are conspicuous and when they are separated by an interval of 0.129 of a second or more.

Apart from the recognised quicker descent of pressure throughout the whole of the latter periods of the pulse cycle in aortic regurgitation, there appears to be no especially steep phase of descent which warrants the application of the term "collapse" to such pulses: if such a term is warranted, then it applies especially to that phase of the pulse which precedes the dirotic incisure, and consequently it does not appear to be associated directly with regurgitation through the aortic valves.



TABLE I.

*Normal curves.*

	Blood Pressure.	Upstroke to half-way point on upstroke.		Upstroke to summit of primary wave.		Upstroke to predicrotic summit.		Primary summit to predicrotic summit.		Pulse rate.	
		Arm horizontal.	Arm vertical.	Arm horizontal.	Arm vertical.	Arm horizontal.	Arm vertical.	Arm horizontal.	Arm vertical.	Arm horizontal.	Arm vertical.
F. 51*	125 80 $\frac{1}{2}$	·046 $\frac{1}{2}$	·044	·111	·108	—	—	—	—	67	72
S. 54	120 86	·038	·042	·095	·118	·234	·232	·139	·114	62	63
T. 55	112 80	·047	·046	·103	·129	·233	·238	·130	·109	75	83
J. 56	130 90	·035	·047	·098	·130	·233	—	·135	—	70	73
M. 58	128 80	·031	·042	·089	·101	·234	·231	·145	·130	78	72
G. 101	102 70	·051	·050	·129	·129	·241	·239	·112	·110	66	63
C. 102	120 60	·033	·051	·091	·101	·268	·266	·177	·165	66	70
F. 103	120 70	·040	·040	·130	·103	·260	—	·130	—	66	71
W. 105	120 70	·042	·051	·110	·146	·281	—	·171	—	49	55
L. 107	132 70	·032	·039	·075	·102	·255	—	·180	—	63	66

\* The letter is the patient's initial, and the number that of the record in the series.

† Each figure in this and succeeding tables is an average of three measurements.

‡ Systolic and diastolic auscultatory readings.

TABLE II.

*Class I. Aortic curves.\*—Very abrupt upstroke with rapid oscillations.*

	Signs.	Clinical description of pulse.	Pulse rate.	Blood pressure.	Beginning of upstroke to half-way point on upstroke (sec.).	Beginning of upstroke to summit of primary wave (sec.).	Average duration of each oscillation (sec.).	Rate of oscillation per sec.
S. 47	Diastolic murmur† at aortic cartilage, transmitted down sternum.	Conspicuous water-hammer, ill sustained; increased excursion with suggestion of thrill in vertical position.	83	180/40	·006	·081	·023	44
M. 44	Diastolic murmur† at aortic cartilage.	Water-hammer, ill sustained; a tendency to thrill in vertical position.	70	148/40	·006	·079	·022	46
F. 73	Diastolic murmur† at aortic cartilage.	Water-hammer; bisferiens.	61	160/38	·010	·092	·018	56
B. 64	Diastolic murmur at aortic cartilage.	Conspicuous water-hammer; pulse inclined to thrill in vertical position.	83	194/70	·018	·100	·019	53
D. 78	Diastolic murmur† at aortic cartilage.	Conspicuous water-hammer; ill sustained.	87	80/50	·017	·031	·021	48

\* Curves taken with arm held vertically.

† A systolic murmur also was audible at the aortic cartilage in most cases.

TABLE III.

*Class II. Aortic curves,\* Abrupt upstroke, single peak.*

—	Signs.	Clinical description of pulse.	Pulse rate.	Blood pressure.	Beginning of upstroke to half-way point of upstroke (sec.).	Beginning of upstroke to summit of primary wave (sec.).
D. 45	Diastolic murmur at aortic cartilage.	Full water-hammer, ill sustained; increased excursion and tendency to thrill in vertical position.	96	158/40	-024	-064
R. 41	Diastolic murmur at aortic cartilage.	Almost full water-hammer with a suspicion of double shock.	75	170/50	-030	-081
B. 64	Diastolic murmur at aortic cartilage.	Conspicuous water-hammer; inclined to thrill in vertical position.	82	194/70	-027	-069
G. 87	Diastolic murmur at aortic cartilage.	Quick upstroke; ill sustained; tendency to thrill in vertical position.	75	160/60	-025	-073
T. 108	Diastolic murmur at 3rd left cartilage.	Moderately full water-hammer; quick rise, sustained for a short while, then falls away. Double peak not felt.	84	190/50	-028	-070

\* Curves taken with arm in horizontal position.

TABLE IV.

*Class III. Aortic curves,\* - Abrupt rise, two peaks, oscillation on upstroke.*

—	Signs.	Clinical description of pulse.	Pulse rate.	Blood pressure.	Beginning of upstroke to half-way point of upstroke (sec.).	Beginning of upstroke to summit of primary wave (sec.).	Beginning of upstroke to summit of second wave (sec.).	Primary summit to second summit (sec.).
R. 99	Diastolic murmur at aortic cartilage, transmitted down sternum.	Quick upstroke; large pulse; double top just perceptible; somewhat feeble in vertical position.	73	160/40	-018	-081	-223	-142
G. 97	Diastolic murmur at aortic cartilage.	Large pulse; quick upstroke; double top just perceptible; thrill in vertical position.	74	152/52	-027	-070	-212	-142
F. 73	Diastolic murmur at aortic cartilage.	Water-hammer; bis-furiens.	63	160/38	-040	-107	-263	-156

\* Curves taken with arm in horizontal position.

TABLE V.

*Class I F.\***Abrupt upstroke. Two peaks.*

	Signs.	Clinical description of pulse.	Pulse rate.	Blood pressure.	Beginning of upstroke to half-way point on upstroke (sec.).	Beginning of upstroke to summit of primary wave (sec.).	Beginning of upstroke to second summit (sec.).	Primary summit to second summit (sec.).
S. 36	Diastolic murmur; systolic thrill at aortic cartilage.	Bisferiens.	70	150/50	-017	-060	-236	-176
N. 71	Diastolic murmur; systolic thrill at aortic cartilage.	Quick rise, distinctly bisferiens, tendency to thrill on elevation of arm.	65	134/40	-025	-097	-263	-166
G. 112	Diastolic murmur at aortic cartilage, transmitted down sternum.	Bisferiens, medium size, easily palpable.	60	125/50	-028	-069	-246	-177
P. 110	Diastolic murmur, at aortic cartilage, transmitted down sternum.	Large pulse, sharp upstroke; thrill.	65	195/55	-038	-082	-212	-130
Mc. 77	Diastolic murmur at aortic cartilage.	Water - hammer; slight bisferiens; suspicion of thrill in vertical position.	67	154/54	-031	-085	-231	-146
W. 96	Diastolic murmur at aortic cartilage.	Quick rise; large pulse; suspicion of double top and thrill.	84	160/50	-028	-081	-187	-106
W. 39	Diastolic murmur at base.	Bisferiens.	57	120/70	-044	-087	-116	-129
R. 67	Diastolic murmur at base.	Bisferiens, sudden upstroke felt from time to time; well sustained.	63	190/70	-041	-084	-153	-169
H. 61	Diastolic murmur at aortic cartilage; systolic thrill.	Bisferiens; upstroke quicker than normal.	49	140/80	-042	-105	-287	-182
W. 109	Diastolic murmur at aortic cartilage.	Small pulse; bisferiens.	51	125/65	-042	-082	-260	-178

\* Curves taken with arm in horizontal position.

TABLE VI.

*Class V. — Relatively slow upstroke; two peaks, the second higher.\**

—	Signs	Clinical description of pulse.	Pulse rate.	Blood pressure.	Begin-	Begin-	Ana-
					time of upstroke to aortic summit (sec.).	time of upstroke to highest summit (sec.).	erotic to highest summit (sec.).
C. 63	Diastolic murmur; pulmonary cartilage.	Sharp upstroke; pulse suggestive of bisferiens; not a big water-hammer even when arm is vertical.	68	200 70	-078	-204	-123
S. 82	Diastolic murmur and thrill at aortic cartilage.	Slow rising; double peak the second higher.	51	150 70	-082	-253	-171
K. 69	Diastolic murmur at aortic cartilage.	Slow rising; first half of upstroke quicker in vertical position.	51	170 40	-055	-216	-161
J. 66	Diastolic murmur; systolic thrill at aortic cartilage.	Slight water-hammer double topped, the second higher.	65	120 60	-093	-219	-126
D. 65	Diastolic murmur; systolic thrill at base.	Slow rising; small, no anaerotic notch.	59	140 80	-090	-237	-147
M. 90	Diastolic murmur at base.	Anaerotic.	55	152 90	-100	-266	-166
R. 91	Diastolic murmur; systolic thrill at aortic cartilage.	Anaerotic; double topped pulse distinctly anaerotic in vertical position.	50	160 140	-080	-247	-167
B. 94	Diastolic murmur; systolic thrill at base.	Bisferiens, not a large pulse for aortic disease; peak sequel.	60	152 50	-087	-232	-115
J. 111	Systolic thrill at base.	Anaerotic.	78	130 70	-091	-213	-122

\* Curves taken with arm in horizontal position.

TABLE VII.

*Class VI. — Relatively slow rise; single fluid peak.\**

—	Signs	Clinical description of pulse	Pulse rate.	Blood pressure.	Begin-	Up-
					time of rise to half-way point on upstroke (sec.).	stroke to summit (sec.).
A. 72	Diastolic murmur at aortic cartilage.	Water-hammer; single peak.	69	110 40	-049	-131
B. 75	Diastolic murmur at 4th left inter-space.	Slow rising; anaerotic (?)	87	98 70	-053	-126
L. 49	Diastolic murmur at aortic cartilage.	<i>Horizontal</i> : Fully developed, Corrigan; sudden upstroke, fairly well sustained. <i>Vertical</i> : Sudden upstroke increased; thrill most probably not present; moderately full water-hammer.	82	220 58	-043	-110

\* Curves taken with arm in horizontal position.

TABLE VIII.

Table of measurements of pulses in aortic disease, comparing records taken with arm in horizontal and in vertical position.

Class.	Upstroke to half-way point on upstroke (sec.).		Upstroke to highest peak (sec.).	
	Horizontal.	Vertical.	Horizontal.	Vertical.
I. 78	·035	·017	·090	·031
64	·021	·018	·072	·100
47	·022	·006	·058	·081
44	·026	·006	·089	·079
73	·040	·010	·107	·092
II. 87	·025	·013	·073	·115
64	·027	·019	·069	·099
41	·030	·033	·081	·079
45	·024	·010	·064	·051
99	·018	·027	·081	·070
108	·028	·028	·070	·083
III. 99	·018	·027	·081	·070
97	·027	·026	·070	·067
73	·040	·010	·107	·092
IV. 36	·017	—	·060	—
71	·034	·025	·084	·098
112	·028	·029	·069	·081
110	·032	·038	·081	·082
77	·031	·040	·085	·126
96	·028	·027	·081	·082
39	·044	—	·087	—
67	·041	—	·084	—
61	·042	—	·105	—
109	·042	·030	·079	·081
V. 63	·031	·026	·203	·211
82	·039	·079	·253	·274
69	·026	·040	·216	·203
66	·063	·058	·219	·175
65	·057	—	·237	—
90	·068	·073	·266	·243
91	·057	·047	·247	·233
94	·045	·035	·232	·243
111	·033	·055	·087 (·203)	·213
VI. 72	·046	·049	·110	·131
75	·053	—	·126	—
49	·043	·043	·110	·154

\* 0·203 of a second is the interval between the upstroke and the second summit, which is distinctly less in amplitude than the first summit with the arm in the horizontal position. The reverse is true with the arm held vertically.

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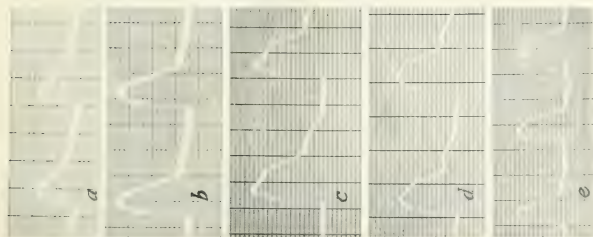


FIG. 2.

FIG. 2. Class I. Curves showing abrupt rise, rounded summit, steep fall preceding diastolic notch, and a series of oscillations on upstroke and platform. Records taken with the arm held vertically. (a) S. 47; (b) M. 41; (c) P. 64; (d) P. 73; (e) P. 78, in Table II.

FIG. 3. Class II. Curves showing a relatively sharp and big rise, a single summit with a relatively small second peak on the downstroke, or a rounded summit. (a) P. 45; (b) P. 41; (c) P. 64; (d) G. 87, in Table I.

FIG. 4. Class III. Curves showing a relatively sharp rise, two consecutive summits, the first considerably higher than the second, and relatively no oscillation or beat from systole on the upstroke. (a) R. 99; (b) G. 97; (c) P. 73, in Table IV.

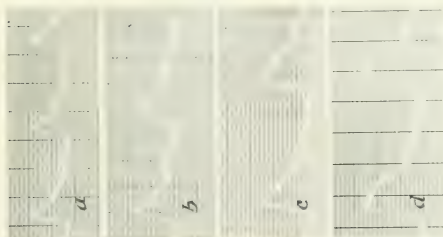


FIG. 3.

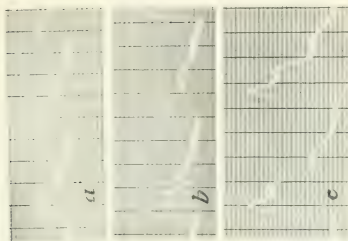


FIG. 4.







Fig. 5.



Fig. 6.

Fig. 5. Class IV. Curves showing a relatively sharp and big rise, with two conspicuous summits of almost equal height. Sometimes there is a distinct vibration on the upstroke. Curves of this type belong to the bisferiens group. (a) S. 36; (b) N. 71; (c) G. 112; (d) P. 110; (e) Me. 77; (f) W. 96; (g) W. 39; (h) R. 67, in Table V.

Fig. 6. Class V. Curves of small pulses, rising relatively slowly. There are two prominent peaks, the second of which is a little or distinctly higher. Records of this type belong to the anacrotic group. (a) C. 63; (b) S. 82; (c) K. 69; (d) J. 66; (e) M. 90; (f) B. 91; (g) R. 94, in Table VI.



## ARBORIZATION BLOCK.

By ALAN N. DRURY.\*

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IN 1916 Oppenheimer and Rothschild,<sup>1</sup> as the result of the observations of a series of cases, described an abnormal and permanent form of electrocardiogram, which they considered to be associated with a very definite form of myocardial involvement.

The abnormalities of the electrocardiogram described affected chiefly the *QRS* group, and were as follows :—

The duration of the *QRS* complex was abnormally prolonged beyond the normal limit of 0.1 of a second. The *R* wave was to be found notched, or the ascending or descending limb splintered. The typical diphasic curves, with the large waves of experimental bundle-branch block, were absent, and, in contradistinction, in many cases low voltage curves were obtained in all three leads. The myocardial involvement, associated by them with this form of electrocardiogram, was found on post-mortem examination to be due to lesions produced primarily by coronary artery sclerosis with closure of the anterior descending branch of the left coronary artery. Such a lesion produced a patchy sclerosis, widely disseminated, but confined for the most part to the endocardial and subendocardial layers of the ventricular musculature. The changes were much more conspicuous in the left than in the right ventricle, and affected chiefly the septal wall, producing thinning or aneurism of the left ventricular wall. Such a sclerosis, as they found post-mortem, they considered had affected the Purkinje network, and had produced a serious conduction disturbance in the tissues beyond the termination of the right and left branches of the atrio-ventricular bundle; a conduction disturbance which showed itself in the above mentioned changes in the electrocardiogram. Altered conduction through the arborization of the Purkinje network giving rise to the bizarre electrocardiogram, they called "arborization block," and maintained it was a very definite condition and to be recognised easily. The prognosis of this condition they stated to be unfavourable.

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\* Working on behalf of the Medical Research Council.

Again, in 1917, Oppenheimer and Rothschild<sup>5</sup> amplified their original statement by a description of sixty-two cases. They drew the same conclusions both as to the electrocardiographic and post-mortem findings. The serious nature of the condition was again emphasised.

In 1918 Carter<sup>1</sup> described a series of cases which gave similar electrocardiographic findings to those described by Rothschild and Oppenheimer. He amplified the electrocardiographic findings by drawing attention to the

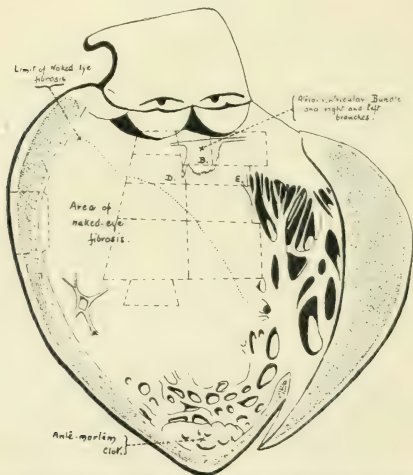


Fig. 1. Diagrammatic drawing of the left ventricle (two-thirds natural size), showing the area of naked eye fibrosis, the blocks cut histologically, and the distribution of the atrio-ventricular bundle and its branches.

direction of the notched *R* waves, which were found to be opposite in leads *I* and *III*, and to the *T* wave being in a direction opposite to the initial peaks. The examination of the heart post-mortem showed that they conformed both on naked eye and histological examination to the type designated by Rothschild and Oppenheimer as cases in which the electrocardiogram should show "arborization block." Complete histological examination of the atrio-ventricular bundle showed that definitely focal

lesions involving the main stem and its branches might be found in cases giving the low voltage curves characteristic of the diffuse sclerosis.

In 1918 Willis<sup>11</sup> described 138 cases of this same condition and also brought forward clinical signs and symptoms which are to be found associated with it. The hearts, post-mortem, showed disease of the sub-endocardial myocardium. Neuho<sup>12</sup> and Wedd<sup>13</sup> have also reported cases, and drawn similar conclusions. The condition "arborization block," as reported in the above papers, would appear to be quite definite. We are led to believe that it is easily recognisable by the bizarre form of electrocardiogram, that the prognosis can be made with a fair degree of certainty, and that the post-mortem findings may be completely anticipated. The case herein reported throws doubt upon the first and last of these conclusions. It at any rate gives proof that there are exceptions, and that lesions, such as are described by Rothschild and Oppenheimer and others, may be found post-mortem, and yet the electrocardiograms obtained may show no departure, such as they describe, from the normal type.

Rothschild and Oppenheimer's hypothesis is twofold. In the first place they believe that an obstructive lesion of the descending branch of the left coronary artery interferes with the conduction power of the corresponding arborization in the left ventricle. In the second place, they believe that failure of conduction through this portion of the arborization yields characteristic electrocardiograms of the form described. Combining the two hypotheses they believe that obstruction of the descending branch of the left coronary gives rise to the characteristic electrocardiograms.

### *Clinical History.*

The patient, C.P., male, aged 48, first attended University College Hospital, on November 20, 1919. He complained of a dull præcordial pain which radiated down his left arm to the elbow, palpitation and breathlessness which he first experienced in 1917, and latterly brought on by slight effort. His family history gave no evidence of rheumatic fever or chorea. He had been a healthy man. There was no evidence or history of syphilis. He presented no signs of venous congestion. The heart was not enlarged, and there was no evidence of a valvular lesion. The rhythm was irregular. An electrocardiographic record was taken at this date.

He was seen next on January 8, 1920. There was no change in the signs or symptoms. On February 19, 1920, he reported again and said that for the preceding two weeks he had been much worse. At this date he showed conspicuous congestion, ears, skin and neck and tongue were cyanosed. His liver was down to his umbilicus. His heart was a good deal enlarged. An electrocardiographic record was taken on this date. He was admitted into hospital and died eleven days later.

*Post-mortem examination.*

*Naked-eye examination of heart.*—The post-mortem examination of the heart of this case showed conspicuous and easily recognisable pathological changes.

In the pericardial cavity were several ounces of clear fluid. The heart weighed 18 ounces. On the external surface of the heart were several milk-like spots on the ventricular surfaces. One, about the size of a shilling, was situated at the junction of the ventricles posteriorly, and another on the conus.

The right auricle was much dilated. There were many ante-mortem clots between the trabeculae, some of which had become cystic in their centres. The right ventricle was also dilated. The muscular walls appeared healthy. Both the tricuspid and pulmonary valves were normal. The left auricle was dilated. No clots were found in it. The endocardium showed thickening over the whole surface.

The left ventricle was dilated and its wall was thin. Extensive fibrosis of the muscular tissue at the apex of the left ventricle with thickening and fibrosis of a corresponding area of endocardium, was seen. The area of fibrosis, about  $1\frac{1}{2}$  inches in diameter, extended upward on the septum to within three quarters of an inch of the aortic valve. This fibrotic thickening of the endocardium was very dense and overlay a sheet of almost cartilaginous fibrous tissue, which sent processes into the muscle, thus reducing its thickness. The lateral wall of the left ventricle at its junction with the septum was also involved. At the apex was an adherent ante-mortem clot about half an inch in thickness. The aortic valves showed very slight traces of thickening and appeared competent. The mitral valves admitted three fingers.

The aorta showed scattered atheromatous patches, these becoming more diffuse around the coronary opening and the sinuses of Valsalva. The right coronary artery was patulous and dilated: large patches of atheroma were scattered throughout its length. These atheromatous areas ended at the posterior descending branch.

The left coronary artery. The orifice of this vessel was small. Near its origin it divided into two branches. The circumflex branch was patent, dilated and atheromatous. The descending branch was stenosed by a fibrotic lesion, probably of a few weeks' standing, which rendered the vessel almost impervious. One half inch lower down the lumen of the descending branch was completely obstructed by fibrosis and calcareous tissue. Thus the macroscopic lesion was identical with those described by Rothschild and Oppenheimer.

*Histological examination.* A histological examination was made of certain parts of the ventricular musculature, as shown in Fig. 1. All gave evidence of the completeness of the lesion affecting the septal and lateral wall of the left ventricle. In all the endocardium was

thickened and fibrosed. Beneath the thickened endocardium of the left ventricle, even in the blocks taken from the parts where no naked eye fibrosis was discernible, a thick sheet of fibrous tissue was found. This sheet varied in thickness in the different blocks cut, extending from one eighth of the total thickness of the septal wall in the upper blocks to two thirds in blocks taken from the centre of the fibrotic area. From this sheet strands of fibrous tissue extended through to the surface of the right ventricle, and in many places formed a network of varying mesh, in which smaller or larger masses of muscle fibres were embedded. A large number of small muscle masses had been walled in by the fibrosis, in some cases lying near the thickened endocardium, and were found in varying degrees of degeneration.

Throughout the blocks, small areas of lymphocytic infiltration were noted. The fibrotic area was well supplied with blood vessels and a large number of extremely thin walled veins were seen in the fibrotic area, close beneath the endocardium.

The atrio-ventricular bundle. This was traced from its origin in the atrio-ventricular node. The main bundle was traced without break from the node to its division into left and right branches. It was thickly surrounded in several parts of its course by fibrous tissue, which radiated into and infiltrated the bundle itself. Evidences of degeneration were noted, but there was no evidence of either a break in the bundle by fibrosis or a focal degeneration affecting the whole cross section of the bundle. The left branch began to curve away from the main bundle early in its course, and this branch extended through a large number of consecutive sections. The bundle branch had a wide origin from the main bundle, and the sheet of bundle tissue thus formed could be traced down to the lower levels of block B with ease, and could be picked up in sections of D and E. Beyond this it was impossible to trace it, for at this level the fibrosis had become much denser, and the issue was confused by the large number of very small muscle masses which had been walled in by fibrosis, and which, lying close under the endocardium, were undergoing varying degrees of degeneration.

It is impossible to comment upon the Purkinje tissue in the lower areas. It might be assumed that the inability to trace the tissue was due to its being destroyed by the dense fibrosis present in the endocardial and subendocardial layer of the ventricular musculature. This is conjecture, and cannot be denied or proved by the histological findings. The bundle and its left and right branches for a distance of one centimetre from the division were unbroken and continuous, although surrounded and infiltrated by the fibrosis present in the heart.

To sum up, the heart presented the following lesions. A complete and old standing occlusion of the anterior, descending branch of the left coronary artery. An intense fibrosis of the septal and lateral walls of the left ventricle.

The main stem of the atrio-ventricular bundle and its left and right branches were unbroken so far as they were followed.

*Electrocardiographic findings.*

Two electrocardiograms were taken from this case. The first was taken on November 20th, 1919, one hundred and two days before death. This curve shows no abnormality save that of ventricular extrasystoles. The *P-R* interval is of normal duration. The *QRS* group of deflections is of normal contour and its duration is not increased. In brief, the features of a normal electrocardiogram with ventricular extrasystoles are exhibited (Fig. 2).

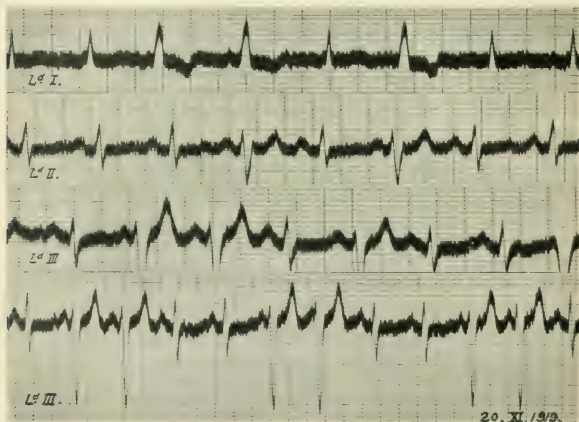


Fig. 2. Electrocardiogram taken on November 20th, 1919. One hundred and two days before death. Time in fifths of a second.

The second curve was taken on February 19th, 1920, eleven days before death. This electrocardiogram shows auricular flutter with a 2:1 block. The ventricular elements of the curve are similar to those previously obtained. The duration of the *QRS* group is well within the limits of normality, being 0.84 of a second (Fig. 3).

In neither of the electrocardiograms do the ventricular complexes present the features described by Rothschild and Oppenheimer and others. There is no notching of the *R* wave, nor splintering of the ascending or



descending limbs. The *QRS* complex has a duration less than 0.1 of a second in both curves.

It may be argued that with flutter present the whole phase is shortened and that the *QRS* complex has suffered in this way. There is, however, no suggestion of lengthening of the *QRS* complex in the first electrocardiograms. At that date, as evidenced by the clinical history and the post-mortem examination of the heart, the cardiac lesions must have been well developed, and the electrocardiogram should have shown some change in duration and form. The *QRS* complex, in the second electrocardiogram, has, moreover, held the contour of the original electrocardiogram unchanged.

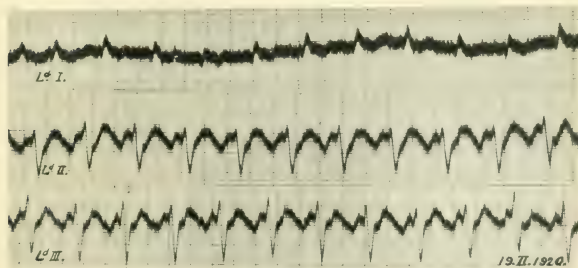


Fig. 3. Electrocardiogram taken on February 19th, 1920. Eleven days before death.

#### *Comment.*

In the case here described the findings are so clear that further observations upon the condition "arborization block" seem not only desirable but essential, before the conclusions drawn in regard to it can be accepted. Both naked eye and histological appearances stamp the heart as identical with those described by Oppenheimer and Rothschild and others: but the ventricular complexes of the electrocardiogram were normal and did not conform to the type which these workers describe.

Experimental evidence is opposed to the view that the type of electrocardiogram which they describe can be definitely associated with lesions of the descending coronary vessel. Smith<sup>8</sup>, in experiments upon dogs, in which the anterior descending branch of the left coronary was ligated and in which the animals were kept alive for periods up to ninety

days, saw no electrocardiograms of the types described by Rothschild and Oppenheimer. The post-mortem examination showed that the fibrosis, both in degree and distribution, was similar in the dog's heart with the fibrosis described in the human subject by the above workers. In later work, in which the lesions of arborization block were imitated by making transverse cuts in the endocardial and subendocardial tissue of the left ventricle, Smith<sup>9</sup> has again failed to obtain electrocardiographic curves of the types under discussion.

It is also well known that the bizarre type of electrocardiogram embodying the features of the so-called "arborization block" may also occur evanescently in other cardiac lesions; Robinson<sup>6,7</sup> has reported such cases. Herrick,<sup>2</sup> moreover, has reported a case in which the heart at post-mortem was found to be identical with the hearts described by Rothschild and Oppenheimer. In this case, the electrocardiogram possessed none of the features associated by these writers with the lesion in question.

The experimental evidence, the case described by Herrick, and the appearance of a similar, though evanescent, bizarre electrocardiogram in many types of cardiac lesions, suggest that other factors than those brought forward by the above workers must be in play to produce these abnormalities of the electrocardiograms. Coupling these facts with the case here reported, it appears desirable that the whole question of so-called "arborization block," supposedly resulting from obliteration of the coronary vessel and its effects upon the electrocardiogram, be reconsidered.

### *Summary.*

A case is described in which on post-mortem examination the heart was found to be identical with the hearts described by Rothschild and Oppenheimer, namely, widespread fibrosis consequent upon closure of the descending branch of the left coronary artery.

The electrodiographic curves obtained from this case presented none of the features described by these workers as characterising this particular lesion.

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## HEART BLOCK INFLUENCED BY THE VAGUS.

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H. M., AGED 51, a farm labourer, was admitted to the Norfolk and Norwich Hospital on March 5th, 1919, under Dr. A. J. Cleveland, by whose courtesy I was enabled to make the observations of March 5th and April 10th.

*Previous History.* He suffered from an attack of influenza twenty years ago, the only illness he has ever had. He has always been strong and healthy. In November, 1918, he had a slight cold, and, very shortly after, two slight fits. He did not go to bed but kept at work until February 25th, 1919. On this date he had four fits, and during the first fell down and hurt himself. Since then he has had many fits daily. He describes the fits as "seizures," which commence with pain in the left side of the abdomen, passing up the left side of the chest and followed by flushing of face, inability to speak, and sometimes unconsciousness. He has passed urine in one or two of these attacks.

*Family history.* His father and mother are strong and healthy. There were seven children in the family, but only three daughters and this son are alive. The second daughter has petit mal. The third daughter had epileptic fits from birth and died in an asylum, aged 42.

*Condition on March 5th, 1919.* A strong, well-built man, with good colour, and a genial, somewhat stupid expression. His pulse rate varies from 60-80 per minute, and is regular for long periods of time. Two or three times during an hour, sometimes more frequently, there is an intermission of the pulse for varying periods. If only a few beats are lost, the patient stops talking, or eating if at a meal, appears confused, with flushed face, and then resumes his normal condition. During the longer intermissions, the attack begins as has been described, the face then becomes more and more cyanosed, the breathing quickens, becomes deeper and finally stertorous, and after two or three seconds, a typical fit commences, with twitching of the face and jerking of the limbs. When the ventricle resumes its beat the symptoms disappear and the patient regains consciousness within half to one minute.

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\*Working on behalf of the Medical Research Council.

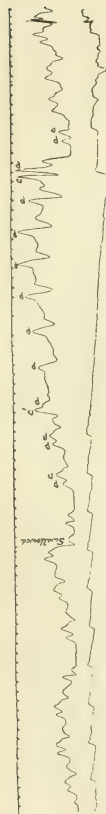


Fig. 1. Effect of swallowing. After an interval of four complete heart cycles the ventricle ceases to beat for a period of 3.4 seconds. The atricular beat continuing unchanged. March 26th, 1919. The time-marker records fifths of a second.

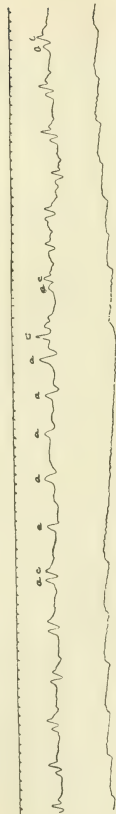


Fig. 2. Ventricular premature beats (not shown on tracing) leading up to a period of failure of ventricular response, taking place as the pulse slowed down after exercise. March 26th, 1919.



Fig. 3. Normal heart sequence and absence of heart block, after an intravenous injection of atropine, gr. 1/33. May 30th, 1919.

The patient volunteered the statement that these attacks were very frequent at meal times, and that he could often bring them on by repeated swallowing.

*The heart* is not enlarged. A soft systolic bruit can be heard at the apex in all postures and in all phases of respiration. His blood pressure is 160-110 (systolic and diastolic).

*Nervous system.* The pupils are equal and react normally. The knee jerks are present. Plantar reflexes are flexor in type. The special senses appear normal. The Wassermann reaction was negative. An X-ray examination during the intermission of the pulse shows cessation of ventricular systole.

*March 26th, 1919.* There were long periods of regular pulse with normal *a-c* interval, rate 60-80. On three separate occasions the patient was asked to swallow, and within 3-4 beats there occurred an intermission of the ventricular beat for a period during which 4-6 regular auricular beats took place (Fig. 1). On one occasion swallowing failed to produce this occurrence. The effect of atropine was not tried. The lapse of ventricular beat also took place, without apparent swallowing, some two or three times during the hour, precipitately and without any previous lengthening of the *a-c* interval. Exercise raised the pulse rate to 105 per minute; as the pulse slowed down there appeared frequent ventricular premature beats, causing a bigeminal pulse and, later, occasional longer periods of ventricular silence (Fig. 2).

*April 10th, 1919.* The *a-c* interval was still normal. The periods of lapse of the ventricular beat were more frequent, occurring 8-10 times an hour. About once in the hour the period would be unusually prolonged, lasting eleven seconds. Unconsciousness supervened after three seconds: fits after 5-8 seconds, ending with the return of the normal pulse, varied by ventricular premature beats. There were still periods of half to one hour in which no intermission of the pulse occurred.

The patient was discharged from hospital shortly after this date.

*May 30th, 1919.* The patient was seen at his home in the country. The pulse was normal, rate 76 per minute, with no lengthening of *a-c* interval, for some 10-20 beats, then occurred failure of ventricular response lasting some 3-5 seconds, followed by another 10-20 normal beats. The longer periods of ventricular silence were also more frequent, occurring as often as once in 10-15 minutes. The longer as well as the shorter periods of ventricular silence were precipitate as before. At 4.30 p.m. atropine, 1/33 of a grain, was given intravenously. Ventricular lapses ceased at 4.40 p.m. At 5.5 p.m. the pulse rate was 85 per minute (Fig. 3). At 5.20 p.m. the first lapse of a ventricular beat occurred, and both this and the succeeding period were interrupted by an idioventricular beat. Following this occurred still longer periods of ventricular quiescence with fits, of which

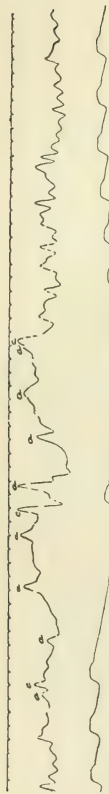


Fig. 4. First lapse of ventricular beat, occurring as the effect of the atropine (shown in Fig. 3) disappeared, interrupted by an idioventricular beat, *a-c* interval normal. May 30th, 1919.



Fig. 5. Complete heart block. August 12th, 1920.



Fig. 6. Effect of atropine *in vivo* (1/45 intravenously). The previous ventricular rate (45 per minute) is unaffected, but an occasional ventricular extrasystole is seen. The auricular rate of 75 is increased to 95 per minute. There is no evidence of any auriculo-ventricular sequence. November 14th, 1920.

the longest recorded lasted twelve seconds. These continued intermittently until the patient went to sleep.

On awaking the next morning, May 31st, the patient noticed the absence of fits, and he has had no more since.

*June 28th, 1919.* The patient attended at the out-patient department of the hospital. The polygraph record suggests complete block. The ventricular rate was 43 per minute and the auricular rate was 110.

*July 31st, 1919.* The patient's condition was unchanged. The ventricular rate was 41 and the auricular rate was 90. The patient went to work the next day and has done a full day's work daily since.

*January 8th, 1920.* The patient's condition was unchanged. The ventricular rate was 45 per minute and the auricular rate 80.

*August 12th, 1920.* The ventricular rate was 38, the auricular rate 80. Exercise did not affect the ventricular rate, but the auricular rate rose to 85 (Fig. 5).

*November 11th, 1920.* The ventricular rate was 48, and the auricular rate 75. After an intravenous injection of atropine, 1/33 of a grain, the ventricular rate was not increased, but the auricular rate rose to 95 (Fig. 6).

### *Discussion.*

The case must be viewed from two aspects, namely, that of the influence of the vagus in producing the ventricular standstill, and that of the existence of a definite lesion of the *A-V* bundle.

It has been shown that on three separate occasions when, as far as could be ascertained, no other factor was operative, determinate swallowing was followed, after a brief interval, by a lapse of ventricular beats for 3-4 seconds. The *a-c* interval remained normal up to the moment of non-response of the ventricle to the auricle. Mackenzie<sup>3</sup> has published a similar case of heart block arising from vagal stimulation excited in a like fashion, but in his case the vagus increased the degree of pre-existing heart block, a prolonged *a-c* interval being already present.

The attacks of heart block could be abolished by atropine, and were thus presumably dependent on vagal stimulation. Laslett<sup>1</sup> describes a similar condition, but with this difference, that in his case the auricles participated equally with the ventricles, so that there was a standstill of the whole heart. The attacks were also abolished by atropine in his patient.

The lapse of ventricular response always occurred without warning, that is, without any preliminary lengthening of the *a-c* interval. A similar feature was recorded by Lewis<sup>2</sup> in a case where the ventricle ceased its beating,

the auricle continuing to beat at its former rate, the *A-V* conduction being generally perfect. In Lewis's case, however, atropine failed to give relief, in contradistinction to this case, where atropine abolished the attacks, it might be said, up to the eleventh hour.

After May 31st, 1919, the patient had no more fits, and the tracings after this date leave little doubt that a condition of permanent complete heart block had supervened. The auricular rate was at first 110 per minute, but, during the course of the next few months it slowed down to 72. The ventricular rate still varies from 38-48. On November 11th, 1920, the intravenous injection of atropine 1.33 of a grain, failed to affect the ventricular rate, which remained at 45 per minute. The auricular rate, however, was raised from 75 to 95 per minute. It would, appear, therefore, that this is a case in which the *A-V* bundle is definitely diseased, the condition being a progressive one, resulting, after a time, in complete heart-block.

During the progress of this condition, as long as there remained intact any fibres of the *A-V* bundle capable of transmitting stimuli, the *a-c* interval remained unchanged. The lapse of ventricular beats was brought about mainly, if not entirely, by vagal influence. This assumption is supported by the result of vagal stimulus by swallowing and of the abolition of vagal stimulus by atropine.

#### *Summary.*

An instance of heart block is described in a man who gave a family history of epilepsy. In the early course of the disease the heart action was for the most part normal, but the ventricle failed to respond to the auricle from time to time for a series of cycles. These periods of ventricular quiescence were associated with unconsciousness or convulsions; the attacks were often provoked by swallowing, and were abolished by atropine: they were provoked through vagal influences. The normal rhythm, so interrupted, continued until complete heart block was displayed; after this event no further seizures occurred.

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## OBSERVATIONS UPON FLUTTER AND FIBRILLATION.

### PART V.—CERTAIN EFFECTS OF FARADIC STIMULATION OF THE AURICLE.

By THOMAS LEWIS and THOMAS F. COTTON.\*

*(University College Hospital Medical School.)*

IN previous articles of this series in which flutter and allied disorders of the auricle have been studied as after-effects of stimulation, these disorders have been induced by stimulating the auricle either with a faradic current or with rhythmic induction shocks. The difference between the two forms of stimulation is one of degree rather than of kind, for the faradic stimulation consists of rhythmic induction shocks of very high rate. In our experiments the rate of the faradic shocks has varied between 2,500 and 3,300 per minute; the rhythmic induction shocks have been used up to rates of 800 per minute, but have usually been employed at rates of 400 to 500 per minute. The two forms of stimulation yield similar after-effects, both provoke flutter, impure flutter and fibrillation in given animals, the only noticeable difference between the two in respect of long after-effects being that in auricles predisposed to flutter, the flutter after-effect is more readily induced in auricles predisposed to it by the relatively slow form of rhythmic stimulation. Otherwise the form of the long after-effect does not appear to be controlled by the nature of the stimulus employed: for in an auricle predisposed to flutter long continued fibrillation cannot be induced by faradic stimulation; neither can flutter be induced in an auricle predisposed to fibrillation by using shocks of lower rate. Such, at all events, is our experience.

The present observations were undertaken to ascertain why faradic or rhythmic stimulation should produce similar after-effects, and have resolved themselves essentially into an enquiry into the nature of the auricular action following almost immediately upon the cessation of faradic stimulation.

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\* Work done on behalf of the Medical Research Council.

If stimulating electrodes carrying faradic shocks are applied to the right auricular appendix or to the region of the inferior vena cava, the disorder in the auricle at the moment stimulation ceases, and for some little while afterwards, is not uniform at different points of its surface. The events are different in that part of the musculature which immediately surrounds the point stimulated and in that part which is more remote.

### *General statement of results.*

If two closely paired contacts are laid upon some portion of the body of the right auricle and the faradic current is turned for a short while into the muscle in the immediate neighbourhood of the contacts, then, when stimulation ceases, the electrogram from these paired contacts almost always presents a series of very rapid oscillations. The oscillations follow each other at rates varying somewhat in different observations: usually the rate is approximately 1,500 to 1,800 a minute: occasionally it may be as high as 2,400 per minute; rarely the rate immediately after stimulation has ended is relatively low, namely, 400 to 500 oscillations per minute.

The initial rapid oscillations, which are the rule in electrograms from the region stimulated, may be regular in form for brief periods, but irregularity of form from oscillation to oscillation or change of form (sudden or gradual) in succeeding periods of a second or a fraction of a second is much commoner. When there is irregularity of form from oscillation to oscillation there is also considerable irregularity in incidence; during the brief periods when the form is maintained the irregularity in incidence is much less and may be almost absent.

The high initial rate of oscillation is not long maintained; the rate falls gradually,\* other features of the oscillations being maintained, until rates from 600 to 350 per minute are reached (see Table I). The rate of 350 to 450 is always reached, providing the after-effect lasts 15 to 20 seconds. The rate has usually fallen to 500, or to a figure somewhat below this, in about 8 to 10 seconds. In a large number of observations upon six dogs† we saw no rate surpassing 500 to 600 a minute, 10 seconds after stimulation had ceased: but we recorded rates as low as 420 to 450 per minute at the end of 3 and 6 seconds. When this stage is reached the electrical events in the region originally stimulated and in that remote from it are not, so far as we have seen, essentially different.

\* A similar falling of rate was observed by Rothberger and Winterberg (Archiv. f. d. ges. Physiol., 1915, cxix, 42-90) in their experiments; but these were conducted under different conditions and the high rate was found, so it would seem from their account, over the whole right auricular surface in the initial phases of the after-effect. The animals employed by these workers were under the influence of pilocarpine or muscarine.

† Anaesthetised fully with morphia, paraldehyde and ether.

TABLE I.

*Illustrating "after-effects" of stimulation.*

Dog.	Type of after-effects in mass of auricle.	Point analysed.	Local events.			Duration of oscillations over 20 to 500 per min. in 1 sec.
J. M.	Pure and impure flutter.	Rt. app.	6 secs.	Rate of oscillations during after-effects.	Less than 8 mm. radius.	About 5 secs.
	Ditto.	L.F.C.	5-14 secs.	2,400, falling gradually through 1,650, 1,200 to 850 to 450 in longer after-effects.	About 14 to 20 mm. radius.	About 10 secs.
J. K.	Impure flutter.	Rt. app.	2-10 secs. and 14½ mins.	1,200, falling to 1,000 or to 450 in longer after-effects.	Less than 8 mm. radius.	About 6 secs.
J. J.	Impure flutter.	Rt. app.	5-8 secs.	1,500, falling through 1,000 to 550.	Less than 16 mm. radius.	About 4 secs.
	Ditto.	L.F.C.	7-10 secs.	1,400, falling to 600	Between 13 and 18 mm. radius.	About 4 secs.
J. I.	Fibrillation.	Rt. app.	4-8 secs.	1,500, falling to 420 in longer after-effects.	About 8 mm. radius.	Almost to end of after-effect.
J. H.	Fibrillation.	Rt. app.	3-12 secs.	1,800-1,200, falling to 450 in longer after-effects.	Between 5 and 20 mm. radius.	About 8 secs.
	Ditto.	L.F.C.	8-12 secs.	1,800, falling to 450 in longer after-effects.	Between 19 and 35 mm. radius.	About 10 secs.
J. G.	Fibrillation.	Rt. app.	7-10 secs.	2,100, falling through 1,500 to 600.	15 mm. radius.	About 6-8 secs.

There is but an incomplete relation between the duration of the very rapid oscillations and the length of the after-effect. When the after-effect lasts some 5 to 10 seconds only, the oscillations in the region stimulated usually persist at rates surpassing 500 to 600 per minute until the normal rhythm is abruptly resumed. Where the after-effect is short, very rapid rates of oscillation may prevail until almost the very end of the after-effect. Thus, rates of 900 to 1,000 have been recorded within a fraction of a second of the actual termination, and rates of 600 (or cycles of 0.1 of a second) at the actual termination. The highest rates (over 1,000), however, are not seen at the actual termination. When the rate is 1,000 within a fraction of a second of the ending of the after-effect a few cycles of longer duration (*i.e.*, 0.1 of a second or longer) are interposed between the shorter preceding cycles and the actual termination. It appears that so long as rates surpassing 900 to 1,000 per second prevail locally, the after-effect in the auricle as a whole will continue; though, providing there is a sufficiently rapid fall from the rate of 1,000, the continuation may be brief. It appears that the termination may come before rates as low as 450 or 500 per minute are reached. It appears also that although the disorder in the auricles generally is initiated by the local disturbance, that the former may persist while the latter is not maintained; in the longer after-effects the special local disturbance ends and the tissue stimulated presents the same apparent condition as the remainder of the auricle. The high rates are not maintained locally for more than about 10 seconds, but the disorder in the whole auricle may be continued for many minutes (see *Dog J K.*, Table I) or even for an hour.

The extent of tissue involved by the very rapid excitation waves is variable. In the same series of experiments it was found, on stimulating a point on the right auricular appendix, that the very rapid deflections were to be obtained over an area of approximately 8 to 10 millimetres in radius. The rate is very similar in simultaneous leads from two pairs of contacts, the one lying at the point stimulated, the other some 8 to 10 millimetres away; but if the second pair of contacts is removed to a greater distance the rate in the corresponding electrogram is conspicuously lower, being usually very similar to that prevailing in the body of the auricle (*i.e.*, 350 to 450 per second).

Upon stimulating the inferior vena cava, the extension has in our experiments been greater. Curves from tissue removed as much as 15 to 20 millimetres from the point of stimulation are often found to exhibit oscillations of the highest initial rate (1,500 to 1,800 per minute: thus, when the inferior cava is stimulated, the area of muscle thrown into this high grade of disorder may spread well up the body of the right auricle, even to the mid-caval region and to the centre of the body of the auricle.

The effects described are those obtained by faradic currents a little in excess of the threshold value. We have not investigated the effect of varying strengths of current upon the extent of tissue so involved.

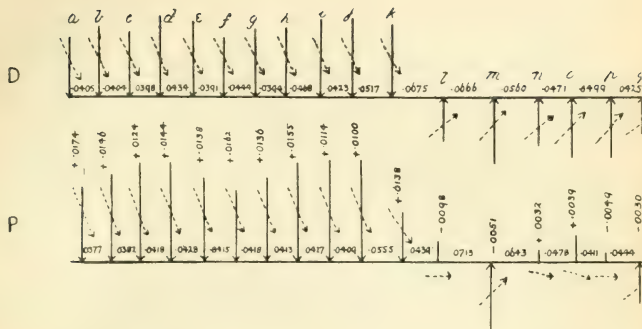


FIG. 1. *Dog JM.* (Record 12.) The arrangement of loading of contacts and their relation to the right of the chart. The chart itself analyses the lettered portion of Fig. 4. The two series of vertical arrows. The position of an arrow, relative to its corresponding base line, indicates downstroke in the record; the direction of the arrow indicates whether the general movement wave was up or down the corresponding pair of contacts. If an excitation wave strikes Z first a downstroke in the curve. The broken arrows indicate the more particular direction of the impress left on both pairs of contacts. The intervals between successive deflections of intervals between corresponding deflections of the two curves are written vertically, indicated

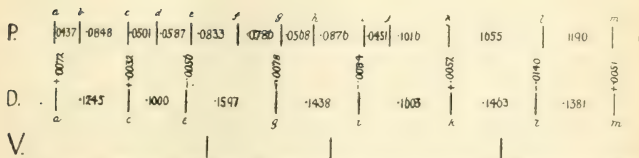
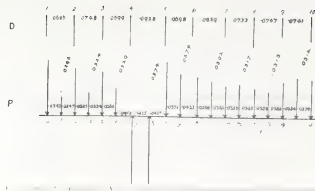
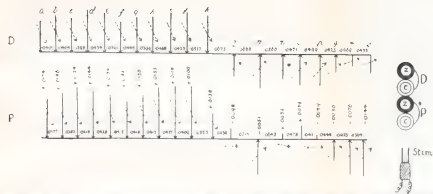


FIG. 3. *Dog JG.* (Record 4.) A chart showing the analysis of Fig. 6. The intrinsic defects



In investigating the extent of tissue involved by means of two pairs of contacts, each pair being connected to a separate recording fibre, it is customary to find the fastest rate exhibited in the curves from both the proximal and the distal pair, or the fastest rate by the proximal pair and a rate of 350 to 450 by the distal pair, according to the distance which separates the pairs of contacts. It is unusual to see oscillations of the fastest rate in the curves from the proximal lead and of an intermediate rate (750 to 900 per minute) in the curves from the distal lead: the change from the highest rate at the point stimulated to the lowest rate which prevails in the main mass of the auricle is abrupt, or relatively abrupt, and the boundary between the most agitated section of muscle and the remainder is fairly sharply defined. On occasion, and on occasion only, when the pairs of contacts are fortunately placed, a relation may be established between the rapid excitation waves recorded by the more proximal and the slower excitation waves recorded by the more distal contacts. Thus a simple 2:1 relation may be seen, broken into from time to time by periods in which the rate in the two curves is equal.

#### *Description of curves.*

To illustrate and amplify the statements of the foregoing general account of what we find, we describe a few selected observations.

*Example 1.* Two pairs of contacts were placed on the body of the right auricle in line with the inferior vena cava. The contacts were connected so that the proximal pair (*P* in Fig. 1) was connected to the bottom string and the distal pair (*D* in Fig. 1) to the top string, as these record in Fig. 4; in each case the *C* contact lay towards the inferior cava. The two *C* contacts lay 8 millimetres apart. The inferior vena cava was stimulated faradically in line with the contacts, and at a point 6 millimetres from the nearest contact (*P C*). Stimulation continued for 10 seconds and was then withdrawn. An after-effect lasting 5 seconds resulted, and part of this after-effect is displayed in Fig. 4. This figure shows the two electrograms and a muscle curve from the right ventricle. The electrograms show a series of very rapid oscillations throughout, the rate being approximately 1,500 per minute at the beginning of the figure, but falling at the very end of the curve to almost half this rate. The after-effect ceased within a second or two of the end of this record. In both electric curves many steep intrinsic deflections are to be seen, and from time to time these appear to be grouped fairly regularly, at other times they are much less regular, both in amplitude and incidence. At no period is the amplitude constant, and from time to time the direction of the deflections becomes reversed. Here is no simple disorder, but a complex one. The measurements of a portion of this figure (the deflections marked *a* to *s* in Fig. 4) are charted in Fig. 1. The intrinsic deflections are represented as vertical arrows in two lines *D* and *P* (curves from distal and proximal pairs of contacts) the

lengths of the arrows representing the heights or depths of the deflections, and their directions representing the directions taken by the excitation waves in passing beneath the contacts which are shown to the right of the chart. Between the arrows the inter-intrinsic intervals are written horizontally in decimal points of a second. The intervals between what are regarded as corresponding deflections in the two curves are written vertically on the chart between the two lines of arrows.

Now the intrinsic deflection  $a$  to  $j$  are amongst the most regular deflections of the whole curve, yet these also vary in amplitude, and on minute measurement display a slight but definite irregularity of rhythm. The maximal differences in their lengths in the two curves amount to 0.0070 and 0.0050 of a second, which is well beyond the possible error in measurement. There is a similar variation in the intervals between intrinsic deflections of the top and bottom curve which are regarded as corresponding, the maximal variation being 0.0074 of a second. Correspondence between intrinsic deflections of the top and bottom curve is thought to be present because the rate is the same, and because shortening or lengthening of the inter-intrinsic intervals in the one curve seems to correspond with similar shortening or lengthening of the intervals in the bottom curve. This is particularly displayed by the lengths of intervals  $jk$  in the two curves. Consider the deflections  $a$  to  $j$  in the two curves as a group. They represent excitation waves which arrive *almost* rhythmically at the contacts, striking the  $Z$  contact of each pair first, and striking the distal before the proximal pair of contacts. These observations are in harmony and confirm the view that the same excitation waves pass both pairs of contacts: they show also that these excitation waves are travelling *towards* the inferior vena cava, the point originally stimulated. The general direction taken by these excitation waves in their passage over the contacts is indicated by the broken arrows of the figure. Up to excitation wave  $k$  the events are relatively regular; but from this point onwards they are not. At cycle  $l$  the interval between distal and proximal deflections changes from a plus to a minus quantity, indicating that the direction pursued by the excitation wave has become changed, now reaching the proximal before the distal contacts; at the same time, the direction of the deflection in the distal curve becomes reversed, a change which accords with this conclusion. From this point onwards the deflections show minor changes in amplitude, form and incidence, the interpretation of which is indicated by the remaining broken arrows. It is supposed that, while the first excitation waves ( $a-k$ ) flowed beneath both pairs of contacts towards the inferior cava, and while the excitation wave  $m$  flowed in almost the reverse direction, in some cycles the direction was not precisely the same for the paired contacts taken individually. Now the precise method of spread at each cycle may not be analysable,\* but such analysis is not necessary to establish the following conclusion.

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\* It is only in some of the curves that the analysis can be taken as far as in the present instance; many show greater complexity.



The muscle in the neighbourhood of the point originally stimulated is thrown into a state of feverish activity: waves of excitation passing over it at a rate equal to or not far below that at which the original faradic shocks entered the muscle. These waves do not follow a constant path, they strike now one contact and now another first of all. For a few cycles they may follow an almost constant path; then the direction changes, a new path having been chosen. Yet many of them are propagated for considerable distances, certainly through at least 8 millimetres of muscle, the distance separating corresponding contacts of the two pairs.

This example is one of many which we possess of the disturbances in the region stimulated: many of the curves which show oscillations of high frequency are more complex than that here used as an illustration, the intrinsic deflections constantly changing their forms, amplitude and direction: even the partial analysis of such curves in detail is at present impossible.

The usual event is to discover very rapid oscillations in the region stimulated, while the curves of axial leads (such as lead *II*) speak of impure flutter or fibrillation in the auricle as a whole. The direct leads from muscle remote from the point stimulated conform to this finding, for the curves from these show relatively slow deflections (rates 350 to 500) varying to some extent or greatly in amplitude and incidence: in other words, the muscle at a distance from the point stimulated is activated by excitation waves which follow each other at rates such as are seen when the auricles, as a whole, are in a state of impure flutter or continued fibrillation. In the former case many of the intrinsic deflections are placed regularly and have a regular amplitude and direction: in the latter case the intrinsic deflections are irregularly placed, vary greatly in form and differ in direction. Curves of the first type have been fully illustrated in Part IV of the present series of articles; curves of the second type will be described in detail in a future article.

*Example 2.* In another after-effect, lasting 8 seconds in the same animal, the point of stimulation was the same: the leading-off contacts were similarly arranged (see Fig. 1) but were moved 7 millimetres further away from the point of stimulation: the nearest contact lay 13 millimetres instead of 6 millimetres from the point stimulated. A record, taken during the early part of the after-effect, is shown in Fig. 5. The curve from the proximal lead (*P*) is very similar to the curve of Fig. 4. Very rapid oscillations (rate approximately 1,500 per minute) are seen throughout the curve: these exhibit irregularity in amplitude and at times in direction. In curves from the distal lead the oscillations are of slower rate (approximately 750 per minute): they are also irregular in their incidence. A portion of this curve, intrinsic deflections *a* to *x*, is charted in Fig. 2, upon which the measured intervals are written. The direction of the intrinsic deflections in this record is not always clear, especially is that so in the curve from the distal lead: consequently the chart expresses the events in simplified form.

It will be evident, nevertheless, that there is correspondence between the intrinsic deflections in the two curves, alternate deflections in the proximal curve being related at sufficiently uniform time intervals to successive deflections of the distal curve. It appears that in both this and the last example an area of approximately 14 millimetres radius was fully affected by stimulation: in the case of the last example, both pairs of contacts lay within this radius, and both gave records of very rapid oscillations. When the four contacts were moved further from the point stimulated (so that the nearest contact lay 13 millimetres from the point stimulated) the distal contacts fell by good fortune outside this area while the proximal contacts remained within it: consequently, the latter alone yielded a curve in which the oscillations appeared at their highest rate. It cannot be concluded from the second record that alternate excitation waves flowing under the proximal contacts were transmitted from these to the muscle under the distal contacts, for the direction taken by the former waves was, as a rule, away from the distal contacts; but it is sound to conclude that the area of chief disturbance was limited to a given radius, and that the surrounding muscle in contact with this responded to waves of excitation received from it at a reduced speed, the actual relation of rate being as 2 to 1.

*Example 3.* In this experiment the auricle was examined in a somewhat different fashion. Instead of using paired contacts on the auricle, single contacts were placed on that chamber, 4 millimetres apart, and in line with the point stimulated, namely, the right appendix, and about 15 millimetres from it. Each of these (Z) contacts, which we may term proximal and distal respectively, was paired with a second (C) contact resting on the body wall. This manner of leading off presents a disadvantage, in that all the intrinsic deflections are upright in the curves irrespective of the direction in which the excitation wave is travelling, and consequently no clue is obtained as to the course of the excitation wave from the form of the curve; often, however, as in the present instance, this disadvantage is more than counterbalanced by the certainty with which the intrinsic deflections are recognised, curves taken with single contacts on the actual muscle being usually much simpler to analyse than those obtained from paired contacts. The single contact lead also allows two points in nearer proximity to each other to be investigated.\*

Repeated stimulation of the auricular appendix with a faradic current yielded short after-effects consisting of fibrillation, as shown by lead *II*. Fig. 6 was taken after such an after-effect had lasted some 10 seconds; and the record is from the central part of this after-effect; by good fortune the contacts have been so placed that one (P) lay on the extreme edge of the tissue involved in the local disturbance, while the other (D) lay off it. The intrinsic deflections *a*, *c*, etc., are seen in both curves as sharp upward movements, often preceded by dips of lesser or greater extent. Over

\* Another difference which appears between the two methods of leading is that the ventricular effects are much more prominent in the single-contact lead.

portions of the records these deflections are of equal rate, but over the earliest portion (*a* to *k*) and again for a short while near the end (*l* to *x*), the deflections are much more frequent in the proximal than in the distal lead. The curve, as will be observed, is complicated by prominent ventricular elements (numbered 1, 2, 3, etc.): these always occur simultaneously in the two leads and may be identified as ventricular by comparing the times of their occurrence with the upstroke of the myographic curve (the lowest in the record).

The two series of intrinsic deflections have been measured and charted in Fig. 3, the inter-intrinsic intervals of the single curves being written horizontal, and the intervals between corresponding deflections of proximal and distal curves being written vertically. In each curve the intrinsic deflections occur at irregular intervals: but there is an obvious relation between members of the proximal and distal series, for the inter-intrinsic intervals of the two series vary together in length. There is, however, some variation in the length of intervals between corresponding deflections in the two curves: sometimes these intervals are minus and sometimes they are plus quantities, but the degree of variation is slight compared with the change in the intervals between succeeding deflections. In the earlier portion of the curve, despite these variations, the relation of proximal and distal intrinsics is such as to establish the presence of a 2:1 block. Similar, though less distinct, evidence of the same event is seen towards the end of the record (deflections *l* to *x*).

The record shows the events at the very edge of the tissue especially disturbed by faradisation, and shows clearly that the bulk of the auricular tissue is guarded by its failure to respond to impulses at the full rate at which they are elaborated beneath the stimulating electrodes. It would seem from this record and that last described that the fall in rate may happen in more than one step. In that instance 2:1 response was established between the tissue reacting to the fastest impulses, there being a reduction of rate from approximately 1,500 to 750 per minute. In the present instance the fall at the border of the disturbed area is approximately from 800 to 900 to 400 to 450 per minute. The rate, in fact, falls to that prevailing over the remainder of the auricular tissue.

Fig. 7 was taken in precisely similar circumstances from an after-effect lasting only 7 seconds. Both proximal and distal electrograms in this figure show corresponding series of auricular deflections (*a* to *o*). In this after-effect either the area especially disturbed was smaller, or the rapid oscillations were of shorter duration. The record is similar to that obtained in continuous fibrillation of the auricle, the intrinsic deflections being irregularly placed, but showing clear correspondence in two leads taken from muscle areas lying 4 millimetres apart. Nevertheless, as in the last condition, the excitation waves pass in different directions relative to the contacts, as shown by the intervals between corresponding deflections in the two leads: these are sometimes plus and sometimes minus quantities.

*Discussion and further observations.*

To sum up the foregoing observations, we may say that when a faradic current is applied to the auricle the muscle beneath the stimulating electrodes and the muscle immediately surrounding this point is thrown into a high state of activity. Excitation waves succeed each other at rates of 1,500 to 2,400 per minute. These excitation waves follow varying and probably re-entrant paths through the area of muscle so affected. The main mass of the auricular tissue is not fully involved in this process, for muscle other than that in the immediate vicinity of the point stimulated appears unable to respond to excitation waves in such rapid succession. As a result of this inability of the tissue the mass of the auricular tissue receives impulses at a much slower rate. Local stimulation at very high rates is not equivalent to stimulation of the whole auricle at these rates, the main mass of muscle is guarded from the majority of the impulses. Thus, it appears that so far as the rate of stimulation affects the subsequent events in the auricle, it is largely a matter of indifference whether this rate is in the neighbourhood of 400 to 700 per minute (the rate used in what has been termed rhythmic stimulation (or whether this rate amounts to 2,500 or 3,300 per minute (the rates used in what is termed faradic stimulation); the mass of auricular tissue receives its impulses at much the same rate in both circumstances; for that reason the after-effects of the two forms of stimulation are similar.

Some points of theoretic interest remain for discussion. It may prove important to attempt to explain :—

(1) Why the auricular tissue is able to respond locally at rates rising to 1,500 or even 2,400 per minute.

(2) Why this condition of rapid excitation is continued for a short while after the faradic stimulus is withdrawn.

(3) Why the condition of rapid excitation subsides within 5 to 10 seconds of the withdrawal of stimulation.

(4) Why the original condition of rapid excitation is local.

(5) And, lastly, the nature of barrier which exists between the local area and the mass of the auricular tissue.

These questions are inter-related. It would seem at first sight that the faradic current exalts the functions of the tissue in the vicinity of the stimulating electrodes. Used at almost threshold strength, the individual shocks could not produce direct response in muscle fibres lying at a distance of 15 or 20 millimetres; on the contrary, these fibres, lying as they do on the circumference of the zone of chief disturbance, are not to be regarded as responding to the electric shocks, but as responding to impulses transmitted from fibres lying

nearer the centre of the zone, unless it be assumed that the reactions of these distant fibres has been enhanced by spread of the stimulating current. It might be supposed that their excitability is raised by this current, though that it not the explanation which we adopt. The explanation adopted is a different one, namely, that the faradic current stimulates not only the auricular muscle, but that locally it stimulates also the vagal nerve endings in the muscle. The significance of this explanation becomes fully apparent when it is known that stimulation of the vagus conspicuously decreases the length of the muscle's refractory period.\* The well-known fact is to be recalled that while the auricles are fibrillating, stimulation of the vagus in the neck greatly accelerates the movement of the auricular muscle and produces over the whole auricle,† a condition very similar to that seen as a local phenomenon in our present experiments. The resemblance is in itself highly suggestive, though it does not suffice. Direct evidence is found in the observation, which we have made repeatedly, that the high grade of local disturbance is entirely abolished if the animal is first atropinised. The contrast between curves taken from a pair of contacts placed on the auricular muscle in the immediate vicinity of the stimulating electrodes, before and after the administration of atropine, is most striking, and is exemplified in Figs. 8 and 9. During the period of stimulation, the rate of response to the faradic current approaches closely to the rate of the faradic shocks, and the same rate of excitation is continued for a little while after the stimulating current is withdrawn, providing no atropine has been given. But after atropine the rate of response is notably lower (four, five or six times lower) during the period of stimulation; and very rapid oscillations are never seen in the after-effects. Usually indeed no after-effect is witnessed‡; but where it occurs it consists of relatively slow movements such as are seen in continuous flutter or fibrillation.

*Example 4.* (One of three experiments.) Paired contacts were placed in the line of the auricular appendix, and stimulating electrodes were fixed within about 2 millimetres and in line with these paired contacts. The events under the contacts were signalled by means of the lower string of the record (Fig. 8), the currents of excitation were signalled by means of the top string of the record.§

A faradic current, composed of induction shocks, following each other at a rate of about 2,600 per minute, was applied through the stimulating electrodes, and the record (Fig. 8) shows response of the auricular muscle at this rate. This rapid action of the muscle continued when stimulation ceased. In the record, the rapidly succeeding excitation waves are maintained

\* Lewis, Drury and Bulger. *Proc. Physiol. Soc.*, Dec. 18, 1920.

† These effects of stimulation will be explained fully in an article which is to follow.

‡ An absence of after-effect of auricular stimulation in the atropinised heart has also been recorded by Winterberg. *Archiv. f. d. ges. Physiol.*, 1908, cxvii, 361.

§ By short-circuiting the primary coil of the inductorium through a high resistance, and leading off from a short section of the wire in this bridge.

throughout, though they begin to fall in rate towards the end of the curve. The after effect continued for a few seconds more and then ceased abruptly.

The second record (Fig. 9) shows the result of a precisely similar procedure after the injection of 1/30th of a grain of atropine sulphate.\* During the period of stimulation the auricle responds relatively slowly and irregularly. The excitation waves are marked in the record by means of small crosses, the fine oscillations being the result of direct escape of the stimulating current into the recording contacts. At the end of stimulation the auricle becomes still at once and shortly resumes its normal slow and rhythmic activity.

It seems quite clear that the initial extreme rate of local response in the unatropinised auricle is produced by reduction of the refractory period of the muscle, which is itself mainly brought about by stimulation of the vagus nerve endings or end branches.† We are able to explain, therefore, why extreme rates prevail around the point of stimulation. We are also able to explain why this original high rate is local, for the vagal mechanism in the auricle will not be stimulated universally. The continuation of the local extreme rate after the withdrawal of stimulation for a period of 5 or 10 seconds and its subsidence after these intervals is also understood, for the vagus mechanism will return to its original state in about these time intervals.

The nature of the barrier between the local area of extreme response and the surrounding muscle, in which movement is much slower, also becomes apparent. Those portions of the muscle in which the vagal mechanism is normal are unable to respond to impulses entering it at rates of much over 600 per minute: the refractory period is too long. Many of the very rapid impulses from the highly excited area will fall during the refractory periods of the muscle of the outlying zones. The process of reduction may occur in a single step: or, as the excitation waves travel through muscle in which the vagal mechanism is less and less affected, the reduction may take place in several stages.

This conception of block, arising out of local differences in the length of the refractory period, is one which we are compelled to accept for the experiments recorded: and we begin to see more clearly the relation between this form of local block and the forms which were described in the third article of this series, namely, block with changing transmission intervals, when the auricle is responding to much lower rates of stimulation. If such block were the result of depressed conduction in the usual sense in which this term is employed, we are at a loss to see why similar conduction changes are not called into play in the circumstances of the present experiments, when excitation waves succeeding each other at a rate of 1,500 or more per minute are conveyed as far as 15 or 20 millimetres. This matter is being more

\* A quantity found in this animal to be more than sufficient to abolish all effect upon the heart of strong stimulation of the vagus in the neck.

† A high rate of response may in itself reduce the refractory period and help towards a final culmination of rate.



fully investigated: it is not impossible that the form of block which displays lengthened intervals up to the point of the missed response, when it is displayed in the walls of the auricle, and is induced by a high rate of stimulation, is also the result of local inequalities of the refractory period. A barrier of refractory muscle may be interposed upon the course of the excitation wave, and as this barrier grows in its extent the wave may be deflected further and further upon a sinuous course, whereby its arrival at the recording contacts is more and more postponed.\*

There remains a single point which still requires explanation. The reason why the local disturbance is continued at an extreme rate seems clear: the local vagal mechanism is still overacting. But it is not yet clear why there is a continuation of any kind. Our explanation is that owing to the reduction of the refractory period in the region of the stimulating electrodes, the re-entry of an excitation wave into muscle through which it has recently passed is facilitated. In other words we consider that the conditions have arisen which permit a circuit movement on a diminutive scale to become established. Such a circuit is not necessarily unvarying: it is not necessarily single. Given variation in the course of the circuit, or given that several such circuits of constant or varying path are established, the irregular succession of excitation waves in the area of maximum disturbances (a definite irregularity, though it may be, and often is, slight) becomes intelligible. We cannot offer proof of such local circuit movement at present, but regard the evidence in favour of it, when coupled with evidence of closely allied phenomena of slower rate and larger scale, as very suggestive.

### *Summary.*

The immediate after-effects of local faradic stimulation of the auricle are described. An area of the auricle having a radius of from 8 to 20 millimetres is thrown into feverish activity (rates of 1,500 to 2,400 per second), which continues for some 5 to 10 seconds after stimulation is withdrawn. To this the remainder of the auricle responds at much slower rates, for the most part at rates of 350 to 500 per minute. The after-effect in the auricle as a whole lasts as long or longer than the high-grade local disturbance.

The explanation of these phenomena appear to be that locally the vagal endings in the muscle are stimulated, and the refractory period of the muscle is thereby locally reduced: it is consequently able to respond locally to the full rate of the faradic shocks while the vagal effect lasts: and these rapid excitation waves are continued as circulating waves locally for a while after vagus stimulation ends. But the remainder of the auricular

\* This appears from recent investigation to be actually the case.

tissue maintains its normal and much longer refractory period and consequently responds slowly.

In given circumstances the auricle is capable of conveying excitation waves, which succeed each other at rates of 1,800 to 2,400 per minute; normal auricular muscle is not capable of conveying such rapid waves.

The reason why the after-effects of faradic stimulation and of rhythmic stimulation of much lower rate are similar is that the main mass of auricular tissue is guarded against the receipt of impulses, succeeding each other very rapidly, by the length of its uninfluenced refractory period.



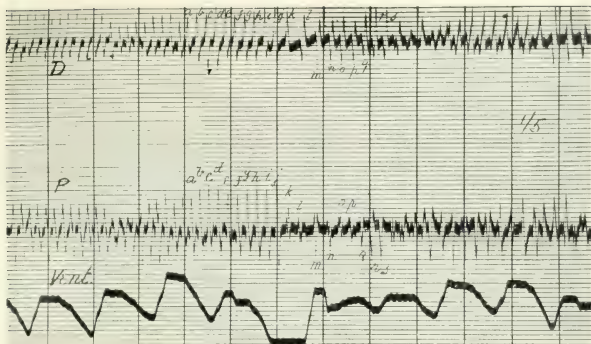


Fig. 4. Dog JM. (Record 12.) Simultaneous electrograms taken from two pairs of contacts placed on the auricle in line with a point of faradic stimulation. The arrangement of the contacts is shown in Fig. 1, in which the lettered deflections of this figure are charted. *D*=curve from distal pair of contacts, and *P*=curve from proximal pair of contacts. The record shows a brief after-effect of stimulation. Below is a myocardiographic curve from the ventricle. Time in fifths of a second.

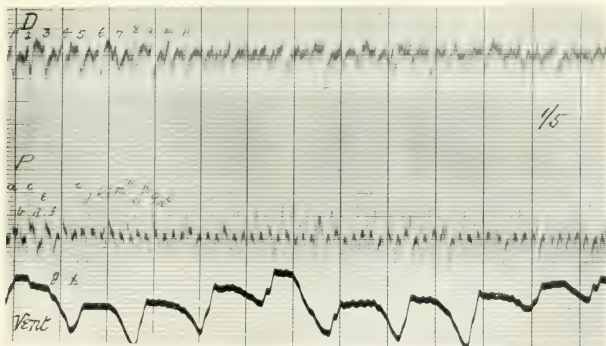


Fig. 5. Dog JM. (Record 10.) Similar curves from another brief after-effect in the same animal. The contacts were similarly arranged, but were placed at a greater distance from the point stimulated. The corresponding chart is shown in Fig. 2. Time in fifths of a second.



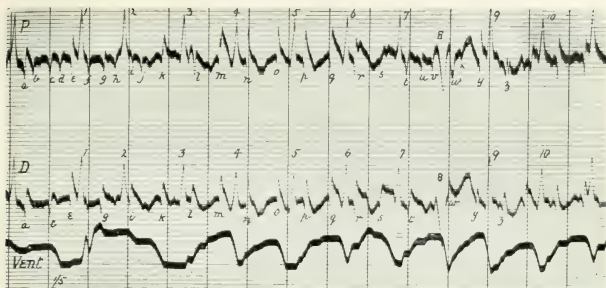


Fig. 6. Dog J.G. (Record 4.) Simultaneous electrograms taken from single auricular contacts, each of which was paired with a second contact on the chest wall. The two auricular contacts lay 4 millimetres apart, and in line with the point stimulated. *P*-curve from contact proximal to and *D*-curve from contact distal to point stimulated. The lettered deflections are auricular and are charted in Fig. 3, the numbered deflections are ventricular and correspond to the ventricular movements displayed by the myoelektrogram (lowest curve of the figure). The record is from a short after effect of stimulation. Time in fifths of a second.

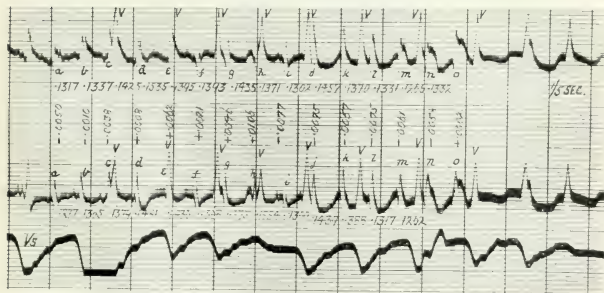
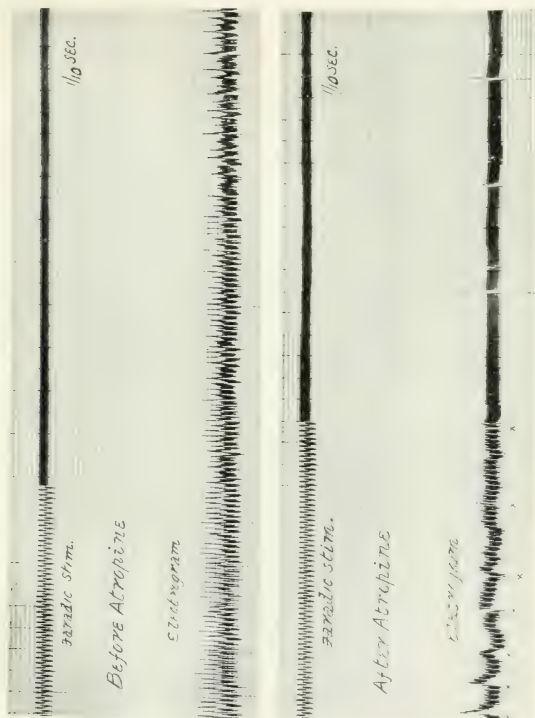


Fig. 7. Dog J.G. (Record 5.) A similar record from the same animal, showing a short after-effect of stimulation. Time in fifths of a second.





FIGS. 8 and 9. Dog L.B. Records 51 and 52. Each record shows above the start of taradic stimulation and below the electrocardiogram from paired contacts placed on the ventricular appendix within a few millimetres of the point stimulated. The records show the influence of atropine upon the reaction to stimulation and upon the after-effect. The latter is absent after atropine. Time in tenths of a second.



## PAROXYSMAL TACHYCARDIA OF VENTRICULAR ORIGIN, AND ITS RELATION TO CORONARY OCCLUSION.\*

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PAROXYSMAL tachycardia is a clinical syndrome characterised by periods of an unusually rapid heart rate of sudden origin and termination. Electrocardiographic studies have shown that the rapid heart rate is associated with an abnormal point of origin of the cardiac impulse. Some portion of the heart other than the sinus node institutes a series of rapidly recurring impulses and therefore assumes the rôle of the cardiac pacemaker. It has also been shown that the abnormal or ectopic point of origin of the impulses may be either in one of the auricles, as is most frequently the case, or in one of the ventricles. The ventricular form of paroxysmal tachycardia is rare, and only a comparatively small number of definite cases have been published. This form of the disorder is of a more serious nature than that of auricular origin, and has in some cases a definite causation. It is therefore important that the two types should be distinguished, which can usually be done by means of electrocardiographic records. It is the purpose of this paper to report four cases of paroxysmal tachycardia of ventricular origin, and to discuss the causation of the paroxysms.

Paroxysmal tachycardia was first separated into that of auricular and that of ventricular origin by Mackenzie,<sup>1</sup> who concluded from a study of venous pulse tracings that the point of origin was not always the same. In the light of further knowledge, however, it can be stated that this method of differentiation is not reliable and cannot be depended upon to separate definitely the two types.

Lewis<sup>2</sup> published the first electrocardiographic records of a case of ventricular paroxysmal tachycardia in 1909, and followed this observation by an experimental study<sup>3</sup> on dogs which demonstrated that this condition sometimes follows ligation of a coronary artery. He found that a rapid succession of impulses sometimes arose in the ventricle when a coronary

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artery was ligated. This procedure was followed either by single extrasystoles arising in one of the ventricles or by a rapid succession of them, which in some cases resulted in tachycardia for definite periods of time. These attacks of tachycardia usually occurred 1 to 1½ hours after ligation, when the nutrition of the ventricular wall had become impaired. The rapid heart rhythm was regular, its onset was abrupt and its rate was from 300 to 420 beats per minute. The paroxysms of tachycardia lasted from a few minutes to half-an-hour or more. Then the normal slow rate returned, or more rarely the ventricles imperceptibly went into fibrillations, causing death of the animal.

Smith<sup>10</sup> made similar observations on dogs in which the ligation of the coronaries was carried out under surgical asepsis. In some cases the smaller branches, in other cases the larger branches, of the coronaries were tied off, and the operative technique was such that the dogs survived the operation and were sacrificed at intervals of from one to ninety days after the ligation. In some of these animals paroxysmal ventricular tachycardia occurred, and was recorded electrocardiographically.

In the progress of some work in our laboratory it has been necessary to clamp the anterior descending branch of the left coronary artery, and the procedure has been followed by isolated ventricular ectopic contractions, ventricular tachycardia, and finally ventricular fibrillation. These various alterations of the heart beat were recorded (Fig. 1).

There is therefore sufficient experimental evidence to show that interference with the coronary circulation may produce ventricular paroxysmal tachycardia.

In order to establish the diagnosis of paroxysmal tachycardia of ventricular origin in man certain data are essential, and it is only by means of electrocardiograms that this type of tachycardia can be differentiated from that of auricular origin. The electrocardiogram must give definite indications that the cardiac impulses producing the high ventricular rate are arising in the ventricles, and this is most clearly shown when a succession of auricular complexes can be made out, occurring independently of, and at a slower rate than, the complexes of ventricular origin. The ventricular complexes are distinctly abnormal in form. The abnormal form of the ventricular complexes alone, however, cannot be taken as absolute proof that the impulses are of ventricular origin, as changes in form may be caused by disturbances of intraventricular conduction. When records made between attacks of tachycardia show that there is no such disturbance, then the ventricular origin of the tachycardia may be considered as very probable, although disturbances of conduction may appear at a high cardiac rate which are not apparent when the heart is beating slowly. This point has been brought out in a previous paper by one of us.<sup>9</sup>

The presence of isolated ectopic ventricular beats before or after a paroxysm is evidence in favour of the tachycardia being of ventricular



origin, especially when the form of the complexes of the isolated beats is the same as the form of those of the paroxysm.

In reviewing the cases of ventricular paroxysmal tachycardia which have appeared in previous reports, only those from which electrocardiograms have been published have been considered. Sixteen cases have been reviewed, and of these only six seem to be undoubted cases when the data which we have described are applied to their diagnosis. They are two cases published by Lewis,<sup>6</sup> one each by Hart,<sup>3</sup> Butterfield and Hunt,<sup>1</sup> Willius<sup>12</sup> and Vaughan.<sup>11</sup>

Six other cases appear to us to be probable cases of ventricular paroxysmal tachycardia. Those published by Hume,<sup>5</sup> one by Vaughan,<sup>11</sup> one by Cohn and Fraser,<sup>2</sup> and one by Willius.<sup>12</sup> Of the other four cases published by Willius<sup>12</sup> one is questionable, and three appear to us to be more likely cases of auricular than of ventricular origin, judging from the published data.

Of the six undoubted cases, all were middle-aged men, except one who was a man of 21. Two of these patients died, one committing suicide a short time after he came under observation, while four cases were still alive three to six months from the time when first seen.

Autopsies were performed on both the suicide and the fatal case. In one, the suicide, atheromata of the left coronary artery are described. In the other the condition of the coronary arteries is not mentioned, but the myocardial lesion which is described is of the type often following a lesion of the coronary arteries, and suggests that such a lesion may have been present.

We have observed four cases which we consider undoubted examples of paroxysmal tachycardia of ventricular origin.

*Case I.* A man of 53 had had syphilis eight years previously. He had received treatment with mercury for three years until he had a repeatedly negative Wassermann reaction. Two weeks before admission to the hospital he applied to the out-patient department on account of shortness of breath on exertion, which he had had for two years, and for a feeling of oppression across the upper chest which had been present for three or four months. At this time his systolic blood pressure was 165 mm. Hg. The urine contained a trace of albumin and many granular and cellular casts.

At 2 a.m. of the night of his admission to the hospital he was awakened by a severe pain in the upper chest followed by a cough with bloody frothy sputum and a persistent precordial pain. He was admitted to the hospital at 4 a.m., at which time he appeared to be *in extremis*. There was definite orthopnea, his respiration being forty per minute, and accompanied by grunting or groaning. He had conspicuous cyanosis of his lips and hands, an ashy pallor of the face and a moist cool "clammy" skin. The pulse was small, rapid, weak and "thready" with a rate of 190 per minute. The systolic blood pressure was 115 mm. Hg., and the diastolic pressure was 90 mm. Hg. The outline of cardiac dulness extended 5 cm. to the right

and 14 cm. to the left of the mid-sternal line. No murmurs were heard, but the heart sounds were weak and embryocardiac. Bubbling râles were present throughout the chest.

Electrocardiograms taken soon after admission showed a succession of abnormal ventricular complexes occurring regularly at a rate of 185 per minute. Occasional waves suggesting independent auricular contractions are seen in the records, but their regularity is not sufficient to establish the existence of an independent auricular action and to determine its rate (Fig. 2).

About ten hours after admission the heart rate was found to have become 120 per minute. The transition from the rapid to the slow rate was not observed. Electrocardiograms taken during the slow rate demonstrated a normal relation of auricles and ventricles, somewhat exaggerated auricular complexes and small abnormal ventricular complexes, entirely different in shape and size from those in the records obtained during the rapid heart rate (Fig. 3). The heart rate rose again to 190 per minute about twenty-four hours after admission, and the patient died two hours later. No records were made during the second period of tachycardia. At the autopsy the heart had an unusual shape, because there was a definite forward bulge in the lower part of the left ventricular wall, which area had a dull grayish colour. This part of the myocardium was that supplied by the anterior descending branch of the left coronary artery. This vessel was found to be completely occluded by a fresh thrombus commencing at a point 1.5 cm. from the origin of the vessel and extending 2 cm. along the lumen. The wall of the vessel was much thickened, and a typical syphilitic lesion was present. The circumflex branch of the left coronary artery showed thickening of its walls and a reduction of the lumen to a diameter of 1 mm. The area of the heart wall supplied by this artery was atrophic and showed an extensive overgrowth of connective tissue. The accompanying figures show the thinning of the ventricular wall (Fig. 4), the thrombosed vessel (Fig. 5), and the gummatous lesion in the vessel wall (Fig. 6).

*Case II.* A salesman of 58 was admitted to the hospital on December 12th, 1915, with dyspnoea, pain in the chest, and tachycardia. Ten years previously he had been told that he had chronic nephritis, and had discontinued the use of protein food and alcohol, which had been used previously, at times to excess. There was no evidence of syphilis.

His illness began two weeks previous to admission to the hospital with a sudden pain in the region of the heart while walking. It was sharp, severe and radiated down the left arm, and was accompanied by a sense of constriction about the chest and difficulty in breathing. He "stumbled home alone," and was given morphine which relieved him temporarily, but the pain returned and persisted. His breathing was said to have been continuously laboured, and cyanosis was observed. He had several attacks before admission, in which the pain in the chest became excruciating, the skin became cold and moist, the pulse rapid, weak and thready. Rusty

blood tinged sputum appeared, and his temperature rose to 101.6°F. Three days before admission to the hospital the patient went into "collapse," and the pulse became very rapid on the day before admission.

On physical examination, at the time of admission, the patient was stuporous, very cyanotic and dyspnoeic. The heart rate was between 180 and 200, the rhythm regular. The outline of cardiac dulness extended 4.5 cm. to the right and 13 cm. to the left of the mid-sternal line. The heart sounds were clear, and except for an accentuation of what seemed to be the first heart sound in the apex region, they were weak and rapid.

Moist râles were heard at both bases posteriorly, but otherwise the lungs were clear. The liver dulness extended 9 cm. below the costal margin, and the abdomen was slightly distended. The systolic blood pressure was 138 mm. Hg. at the time of admission, but fell gradually until it reached 95 mm. Hg. thirty-six hours later. Cheyne-Stokes breathing was noted the day after admission.

Pressure over the vagi and ocular pressure failed to produce any effect on the heart rate. Atropine sulphate (gr. 1.50 hypodermically) produced no change in the rapid ventricular rate.

The heart rate was continuously rapid until December 22nd, eleven days after the onset of the tachycardia. The rate ranged from 185 to 248 beats per minute. No cause for the change in rate was ascertained. During the first week of this period the patient improved distinctly. He became rational, his pain practically disappeared, his lungs became free from râles, and he said he was fairly comfortable. This improvement did not seem to depend on his medication. Strophanthin, 1 mg. intravenously (which to-day we would not deem advisable because of its apparent tendency to throw the ventricles into fibrillation) had no apparent effect on the circulation.

On December 18th the patient complained of fatigue, and his output of urine was much diminished. The phenolsulphonaphthalein output diminished during the period of tachycardia. On December 21st alternation of the pulse was observed, and the heart rate slowed to 180 per minute. On December 22nd the heart rate fell to 120 per minute, while the systolic blood pressure, which had been varying from 110 to 95 mm. Hg., rose to 154 mm. Hg., while the diastolic pressure was 90 mm. Hg. During the period of relatively slow heart rate the patient was worse, being weak, fatigued, and uncomfortable. On December 27th the heart rate again rose to 190 per minute, while the systolic blood pressure fell to 105 mm. Hg. with a diastolic pressure of 95 mm. Hg. The patient seemed better than during the slower heart rate, but no increase in the urine output occurred, and he soon began to have increasing weakness. On January 3rd, 1915, he became unconscious and apparently moribund, and he died on January 4th, eight days after the appearance of the tachycardia. The heart rate again slowed to 120 beats per minute a few hours before death, and then gradually became slower until he died. An autopsy was not permitted.

Electrocardiograms were taken at frequent intervals throughout the illness. Record No. 283, taken on the day of admission, showed the ventricles to be beating at a rate of 221 per minute and yielding complexes of abnormal form. In the first lead small waves of auricular origin, occurring regularly at a rate of 116 per minute, can be made out (Fig. 7). Record No. 297 was obtained on the first day of the relatively slow rate, December 22nd, and shows that sequential beats had been re-established at a rate of 120 per minute. The ventricular complexes are small and distinctly abnormal, but entirely different from those seen in the records obtained during the periods of tachycardia (Fig. 8). Record No. 300 was obtained on the first day of the second period of tachycardia, when the ventricular rate was approximately 190 per minute (Fig. 9). The form of the ventricular complexes is different in the records obtained during the second period of tachycardia from those obtained during the first. In this record the evidence of auricular activity is seen in all leads, and the independence of auricles and ventricles is clearly shown. The auricular rate is approximately the same as that of the whole heart during the period between the attacks of tachycardia. These records clearly demonstrate that this case is one of paroxysmal tachycardia of ventricular origin.

When 1/50 grain of atropine sulphate was given the ventricular rate was shown by electrocardiograms to continue at 195 per minute, while the auricular rate increased from 121 to 137 beats per minute.

*Case III.* A housewife of 53 was admitted to the hospital on October 29th, 1915, complaining of indigestion, heart trouble and pain in the throat and arms. Her general health had always been good. There was no history of a severe infectious disease, or of the use of alcohol or of excessive physical or emotional strain. Although married she had never become pregnant, the cause of sterility being unknown. Her Wassermann reaction proved to be negative with all antigens.

In March, 1912, the patient began to have weakness and abdominal distress after eating breakfast, while in the spring of 1913 she had on exertion an aching or burning in the throat which radiated down the arms, especially the left arm. She said she had had an "all gone, generally depressed feeling," and had had difficulty in climbing stairs. She considered that these symptoms were of gastric origin. After several weeks they improved somewhat, but did not entirely disappear. In December, 1914, the patient had a severe pain in the left side of the chest, which lasted from 20 to 36 hours, and which she was told was pleurisy.

This pain did not recur. In March, 1915, the patient became very "nervous," and was told she had hysteria. On the 8th of March she had a severe pain in the throat and arms, which lasted five or six hours. She remained in bed for ten weeks after the attack. For two months previous to her admission to the hospital the patient had attacks of palpitation of the heart, associated with a feeling of flatulence and with an aching

feeling in the arms. During five weeks previous to admission the attacks of cardiac palpitation became more frequent, occurring about four times a week. They seemed to be precipitated by "eating when tired," and reclining after meals lessened the attacks. A severe attack of palpitation caused her to enter the hospital.

On examination the patient appeared very healthy. She was not in distress, and was very well nourished. There was slight cyanosis of the lips, mucous membranes, and nail beds, and she was slightly dyspnoëic. The heart was beating regularly at a rate of 74. The apex beat was not seen or felt. The outline of cardiac dulness extended 4 cm. to the right and 11.5 cm. to the left of the mid-sternal line. The heart sounds were faint and no murmurs were heard. The systolic blood pressure was 135 mm. Hg., and the diastolic pressure was 90 mm. Hg. The fluoroscopic examination revealed "a somewhat enlarged heart." The abdomen was somewhat distended. There was a slight anemia. The urine showed a very slight trace of albumin and many hyaline and a few granular casts. No other findings of importance were noted. As stated above, the Wassermann reaction was negative.

On the morning after admission the patient had an attack of palpitation similar to her previous ones. It began and ceased suddenly and lasted about half an hour. The heart rate was 180 per minute. During the patient's stay in the hospital the pulse was often noted as irregular, and electrocardiograms showed that the arrhythmia was caused by interpolated premature ectopic beats of ventricular origin (Fig. 10).

On November 3rd an attack of palpitation was brought on by exercise, which was being carried out to test the functional efficiency of the heart, and electrocardiograms were obtained at this time (Fig. 11). The heart rate as revealed by the records was 170 per minute, and the ventricular complexes were abnormal and distinctly different from those seen with the slower heart rate. Auricular waves cannot be identified with certainty, but there is a small wave on the ascending limb of the *T* wave of every other beat in the third lead, which suggests the possibility of a retrograde stimulation reaching the auricles from every other ventricular contraction. This attack lasted only about half an hour. Records made immediately after its cessation show ectopic ventricular beats, two occurring at times in succession (Fig. 12).

This patient had one more attack, lasting from 35 to 40 minutes, on November 19th, when she got up after breakfast, during which the rate was 180. Electrocardiograms similar to those shown in Fig. 11 were obtained.

She left the hospital on November 27th, 1915, feeling much improved, and was able to take care of her husband through an attack of pneumonia during the winter without discomfort. During the spring, about six months after leaving the hospital, she fell dead, apparently without any premonitory symptoms. No autopsy was performed.

*Case IV.* A labourer of 49 years was admitted to the hospital on April 25th, 1918, from the Out-patient department for tachycardia and pain in the chest. He gave a history of syphilitic infection at the age of 17. He had used alcohol moderately, and had had several attacks of acute rheumatic fever. He also gave a history of one previous attack of palpitation of the heart. He said that six days previous to admission he was taken suddenly with a sharp pain in the chest on reclining, which was followed by a thumping of the heart and a choking sensation. He vomited and was unable to sleep. His heart became quiet in two days, but on attempting to walk to his place of work the cardiac symptoms returned and persisted until and after his admission to the hospital, three days later.

On admission he presented an anxious expression with slight cyanosis of the lips, ears, and nail beds. His face was of an ashy hue. There was slight engorgement of the veins of the neck, and moderate dyspnoea with Cheyne-Stokes breathing. Moist râles were heard over the bases of both lungs posteriorly.

Over the heart, in the region of the apex and in the epigastrium, a fluttering or tremulous movement was seen. The outline of the cardiac dulness extended 4.5 cm. to the right and 12 cm. to the left of the mid-sternal line. Both heart sounds were distinct at the base and embryocardiac in character. The heart rate was 230 to 240 per minute. Only one heart sound could be heard at the apex. The heart rate could not be altered by pressure over either vagus nerve or by ocular pressure. The systolic blood pressure was 80 mm. Hg. The diastolic pressure 68 mm. Hg. The abdomen was distended and rigid. The liver extended 7 cm. below the costal margin, felt smooth and was very tender. The pupils reacted sluggishly to light. The knee jerks and Achilles tendon reflexes were exaggerated equally on the two sides. A "seven foot" X-ray plate showed what was interpreted as an extreme degree of aortitis. The Wassermann reaction of the blood was negative, while the spinal fluid gave a moderately strong positive reaction.

Electrocardiograms taken soon after admission revealed abnormal ventricular complexes occurring at a rate of 228 per minute. Accompanying every second complex of the second lead a well defined wave is seen, which seems to indicate that the auricles were beating at a rate of 114 per minute. Auricular waves are less definite in the third lead and cannot be made out in the first lead records (Fig. 13).

The tachycardia ceased two days after his admission to the hospital, having continued with a brief intermission for seven days, and having been apparently continuous for five days. At the time of cessation of the tachycardia the heart beat was irregular for a short period, but when electrocardiograms were obtained the heart was beating regularly at a rate of 82 per minute. There was no delay in A-V conduction. The T wave was inverted in all leads (Fig. 14).

The systolic and diastolic blood pressures were 90 and 60 mm. Hg. respectively at this time, but rose in 24 hours to 105 and 60.



During the period of normal rhythm diastolic and systolic murmurs arising at the aortic orifice were heard, and a thrill could be felt over the second right interspace. The patient was found to have a right-sided hydrothorax, which was drained. He remained in the hospital for one month, and anti-syphilitic treatment with salvarsan and mercury was instituted, and has been continued. The patient can now carry on light work, and has had no return of tachycardia.

During his stay in the hospital numerous electrocardiograms were obtained, and changes in the *T* wave were observed. All leads showed an inverted *T* wave for the first five days after the cessation of tachycardia. Then the *T* wave of the third lead became upright. On the following day the *T* wave of the second lead became flat, instead of inverted. Twenty days later the *T* wave of the first lead was flat, while those of the other leads were upright. No digitalis was administered. Records made at intervals since the patient's discharge from the hospital show normal electrocardiograms with upright *T* waves in all leads. This change in the *T* wave resembles certain findings of Smith<sup>10</sup> after coronary ligation and also those observed by Herrick<sup>1</sup> in a case of coronary thrombosis which he reported. These changes may be taken as a probable indication of myocardial disturbance, possibly secondary to an interference with the coronary circulation.

### *Discussion.*

The four cases which have been described present sufficient evidence, in our opinion, to warrant in each instance the diagnosis of paroxysmal tachycardia of ventricular origin. They were all observed during periods when the heart rate was from 170 to 228 per minute. These rapid rates occurred in paroxysms, and periods of relatively slow cardiac rates were observed in each instance. The transitions between the very rapid and relatively slow rates were, as far as observed, always sudden.

That the tachycardia was caused in each case by a very rapid succession of impulses arising in one of the ventricles was determined by electrocardiograms obtained during the paroxysms and during the periods of relatively slow rate. The ventricular complexes in all records taken during paroxysms are strikingly abnormal, and differ markedly from those obtained between attacks. None of the records taken during relatively slow rates show ventricular complexes which are characteristic of disturbances in the main branches of the intraventricular conducting system. The ventricular complexes of the tachycardia records from all cases resemble those which are obtained when impulses arise in the ventricles, either by single spontaneous ectopic impulse formation or by direct electrical stimulation of the exposed ventricles in animals. In the last case the complexes resemble those produced by ventricular contractions arising from stimulation of the right ventricle, while the curves from the other three cases suggest that the ectopic impulses originated in the left ventricle. The difference in form between

the complexes of the first paroxysm of *Case II* and those of the second paroxysm, is of interest, and is the result, we think, of alteration in the intraventricular conduction rather than of a change in the site of impulse formation.

In two of the cases, the second and fourth, definite evidence of auricular contractions occurring at a slower rate than that of the ventricles is seen in the electrocardiograms, waves denoting auricular contractions being present. In the other two cases evidence of auricular activity during the tachycardia is less certain.

The electrocardiograms taken between the paroxysms of tachycardia show definite abnormalities in all the cases. In the first and second cases the ventricular complexes are unusually small and deformed. They resemble the complexes seen in the case of coronary thrombosis reported by Herrick<sup>1</sup>, and those from another case of coronary thrombosis, confirmed at autopsy, from which we obtained electrocardiograms. The *T* wave is inverted in all leads in *Cases III* and *IV*, in the first lead in *Case I*, and in the third lead in *Case II*, the *QRS* group of waves is not unduly prolonged in any of the cases. The curves from all these cases present evidence of myocardial damage, either from the form and size of the ventricular complexes (*Cases I* and *II*), or from the inversion of the *T* wave in all leads (*Cases III* and *IV*).

In only one case, number *III*, were premature ectopic ventricular beats recorded, and in this case they were unusual, because they were interpolated between sequential beats and because they tended to occur in pairs.

The relation of coronary occlusion to ventricular paroxysmal tachycardia is a point of especial interest in regard to the cases that have been reported and to the phenomenon generally. As has been pointed out, this relationship has been established for animals under experimental conditions. In our first case, where syphilitic changes and a thrombosis of the left descending coronary were demonstrated at autopsy, the tachycardia was apparently the result of changes brought about by occlusion of the coronary artery. In the second case the patient's history is very suggestive of coronary occlusion, especially the sudden onset of the illness with severe pain in the region of the heart radiating down the left arm. This primary attack, and several that followed it, were typical of angina pectoris, so often associated with coronary artery disease. There was no evidence of syphilis, but chronic nephritis, artero-sclerosis, and hypertension were present. The third case is perhaps the one in which there is the least evidence of a lesion in the coronary arteries. The history of this patient which is given in some detail, is suggestive of relatively mild attacks of angina pectoris. The fact that she never became pregnant during her long married life suggests that she or her husband may have had syphilis. The most significant fact, however is her sudden death, which apparently occurred without premonition. Such an occurrence is certainly suggestive of sudden



heart failure, especially of ventricular fibrillation, which in turn points toward a lesion of the coronary arteries.

In the fourth case a definite history of syphilis with an extensive lesion of the aortic orifice is very suggestive of a lesion involving the coronary vessels, especially at their origin. Our first case, is, we believe, the first instance where direct evidence of the association of ventricular paroxysmal tachycardia with coronary occlusion has been obtained, although in two other cases which have been studied by others, lesions of the coronary arteries may have been causative factors.

The relationship between paroxysmal tachycardia of ventricular origin and coronary occlusion is by no means constant. We have recently observed two cases which showed occlusion of the coronaries at autopsy, neither of which had tachycardia of high grade during life.

The prognosis of paroxysmal tachycardia of ventricular origin is distinctly less favourable than that of auricular origin. While three of our four cases died, only one of eight cases of auricular origin have succumbed, as far as we know. In the one fatal case of paroxysmal auricular tachycardia, cardiac failure from other causes apparently produced the fatal issue, and the attacks of auricular paroxysmal tachycardia were only incidental. It is probably upon the serious lesion which calls forth the ventricular type of tachycardia that the unfavourable prognosis of this form of tachycardia depends. However, any disturbance of the heart-beat which has its origin in the ventricles must be of more serious significance than those disturbances arising in the auricles.

Another factor in the prognosis of this type of paroxysmal tachycardia is its tendency to pass over into ventricular fibrillation, which usually means permanent cessation of the circulation and death. This occurred in the dog from which Fig. 1 was obtained. It may have happened in the case of the first and third patients, here recorded, although we have no proof of it in either instance. The symptoms which we have observed in the two groups of cases are much more severe and alarming in paroxysmal tachycardia of ventricular origin than in that of auricular origin.

### *Conclusion.*

Four cases of paroxysmal tachycardia of ventricular origin are described. The diagnosis of this condition depends on the interpretation of electrocardiograms, and certain features necessary for this diagnosis are discussed.

The relationship between this condition and occlusion of the coronary vessels has been proven in animals. This relationship, although inconstant, exists in some of the cases of ventricular paroxysmal tachycardia in man. This relationship was definite in the first case here reported and studied at autopsy, and was probably present in all of our cases.

The prognosis of paroxysmal tachycardia of ventricular origin is more unfavourable than that of auricular origin, and the differentiation of the two types is of practical importance.

We wish to thank Dr. M. T. Burrows for the pathological study of our first case, and also for the photographs illustrating the lesions in this case.

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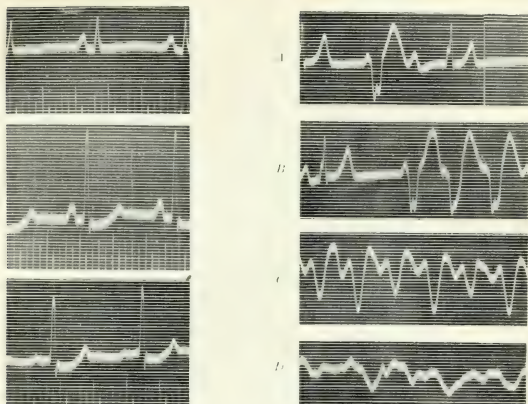


Fig. 1. Electrocardiograms from a dog before and after clamping the anterior descending branch of the left coronary artery. The three usual leads on the left. On the right from above downward are the successive events after the artery was clamped:—*A*. Premature contraction of left ventricular origin. *B*. A succession of contractions of left ventricular origin. *C*. Ventricular tachycardia with alternation in size of complexes. *D*. Ventricular fibrillation, which occurred 45 minutes after the coronary artery was clamped.

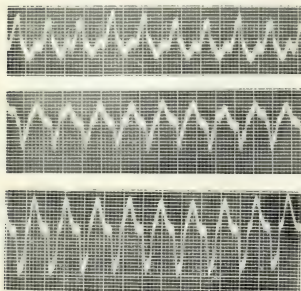


Fig. 2. *Case I*. Electrocardiograms obtained during the first paroxysm of tachycardia. Rate 185 per minute.

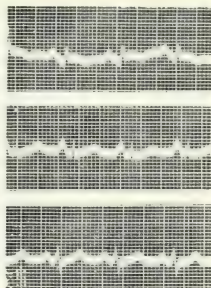


Fig. 3. *Case I*. Electrocardiogram obtained after the cessation of the tachycardia. Rate 120 per minute.



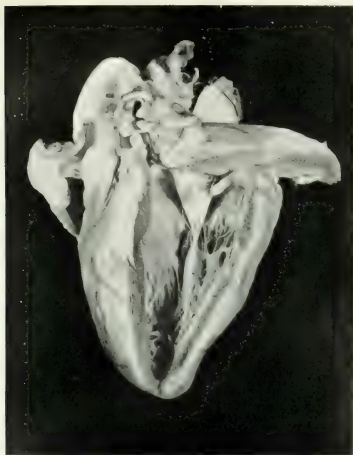


Fig. 4. *Case 1*. Photograph of the heart, showing thrombosis of the anterior descending branch of the left coronary artery, the lesion in the cut surface of the myocardium, and the thinning of the ventricular wall.

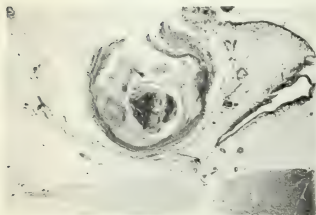


Fig. 5

Fig. 5. *Case 1*. Section of the left coronary artery showing great thickening of the vessel wall, and the thrombus mass.

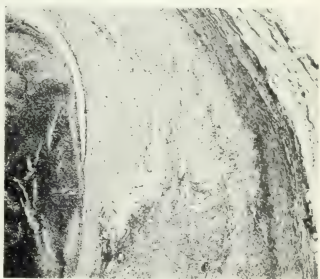


Fig. 6

Fig. 6. *Case 1*. Section of the coronary artery at the site of the thrombus formation. There is much proliferation of the connective tissue of the intima and media, and extensive small round cell infiltration, giving a typical picture of a syphilitic lesion within the wall of the vessel.



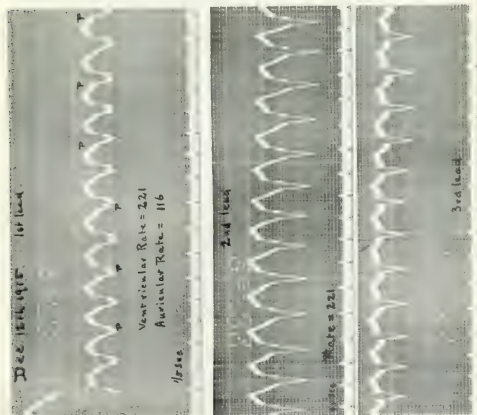


FIG. 7. Case 11. Electrocardiograms obtained on the day of admission to the hospital. Ventricular rate 221 per minute. Auricular rate 116 per minute. Auricular waves last seen in the first lead.

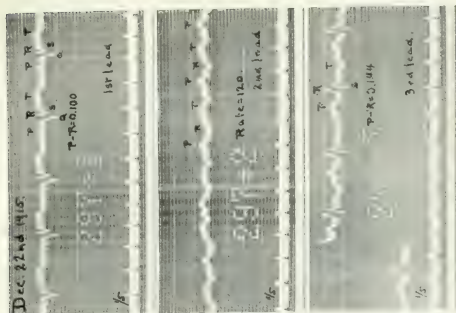


FIG. 8. Case 11. Electrocardiograms obtained on the first day of relatively slow cardiac rate, 120 per minute, 11 days after the onset of the tachycardia. All ventricular complexes of abnormal form, and unusually small.





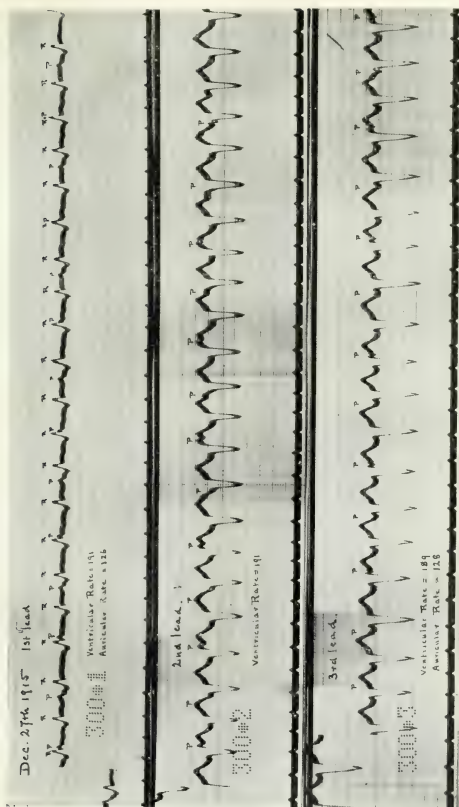


FIG. 11. *Case 11.* ECG tracings obtained on the first day after resumption of the tachycardia. The form of the ventricular complexes is different from that seen in Fig. 7 from the same case. Waves of atrial activity distinct. Ventricular rate approximately 140 per minute. Atrial rate approximately 127 per minute.



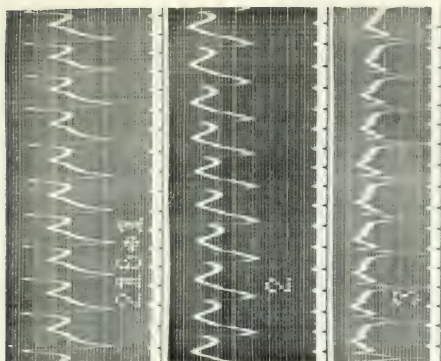


FIG. 11.

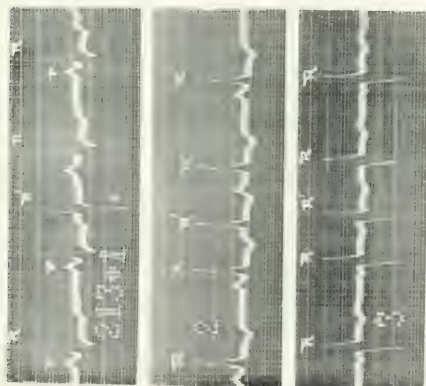


FIG. 10.

Fig. 10. Case III. Electrocardiograms obtained between paroxysms; interpolated premature ventricular contractions marked R.  
 Fig. 11. Case III. Electrocardiograms obtained during a paroxysm of tachycardia. Ventricular rate 170 per minute. Waves preceding the P wave of every other ventricular complex in these three lead less well defined in the second lead.



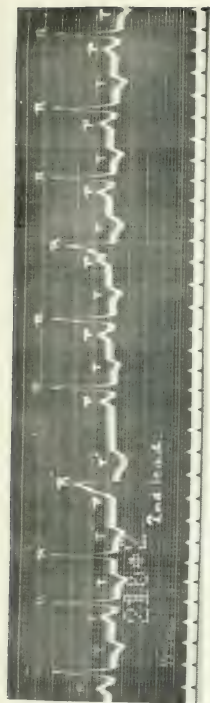


Fig. 12. *Case III.* Electrocardiograms obtained at the termination of the paroxysm shown in Fig. 11. Two premature beats of ventricular origin occur in succession.

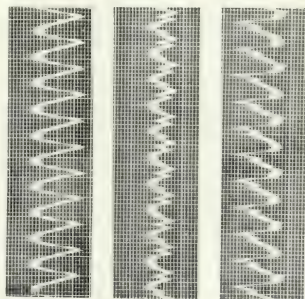


Fig. 13. *Case IV.* Electrocardiogram obtained during tachycardia. Ventricular rate 228 per minute. A well defined wave, probably representing auricular activity occurring with every other ventricular complex is well seen in the second lead.

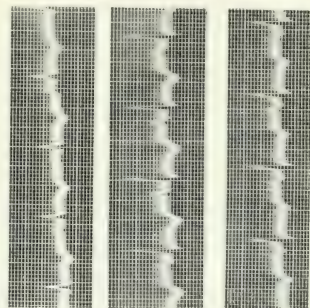


Fig. 14. *Case IV.* Electrocardiograms obtained after the tachycardia had ceased. The *Q* wave inverted in all leads. Heart rate 82 per minute.



# OBSERVATIONS UPON FLUTTER AND FIBRILLATION.

## PART VI.

### THE REFRACTORY PERIOD, AND RATE OF PROPAGATION IN THE AURICLE: THEIR RELATION TO BLOCK IN THE AURICULAR WALLS AND TO FLUTTER, Etc.\*

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#### *Method.*

DIRECT measurement of the refractory period† in the mammalian auricle under different conditions is not so easy a matter as might at first be thought. The period is always brief, in some circumstances very brief, and consequently errors which exceed materially 0·01 of a second render the measurements insufficiently exact. A high grade of accuracy is required. The method of measurement now described is the most accurate which we have found available: but it is suited only to hearts driven artificially at chosen rates, and gives reliable results only when the muscle is atropinised. A second method, described at a later stage, is available when the heart is beating in response to inherent impulses and atropinisation is unnecessary, but it introduces a very material error which may or may not be subject to control.

The apparatus employed is shown diagrammatically in Fig. 1. Two induction coils are used, and the secondary coils are united in a single circuit which passes through the stimulating electrodes. The stimulating electrodes consist of a pair of very small barbed fish hooks, sealed with the smallest possible gap between them. They are hooked into the auricle at the desired point and remain permanently in position. The left-hand inductorium yields rhythmic shocks at any desired rate; these control the heart rate. The right-hand inductorium yields single shocks at irregular intervals; these test the refractory period of the controlled heart beat. The primary coil of the left-hand or controlling inductorium is activated by its own battery and by a rotating interrupter. This interrupter is a heavy metal wheel from which two metal blocks project;

\* Observations undertaken on behalf of the Medical Research Council.

† In speaking of *refractory period*, without qualification, we mean the absolute refractory period.

each of these metal blocks in its revolution makes and breaks a platinum contact key. The one block makes and breaks contact on the circuit which supplies the primary coil; the other short-circuits and opens the circuit of the secondary coil. The contacts are so arranged that the current induced in the secondary coil in response to the break of the primary coil is alone transmitted to the stimulating electrodes;\* a series of single rhythmic break shocks is thus obtained. The right-hand inductorium is supplied by its own battery and is controlled by a tapping key; shocks are transmitted to the stimulating electrode whenever this key is made or broken. Uniting the two circuits of the primary coils are two high resistance circuits, and the string galvanometer is suitably bridged across these. The resistances are so arranged that a small fraction of the current flowing through each primary coil passes through the string, which records photographically the make and break of these currents. In this way the errors arising from magnetic signals are avoided, and the magnitude of the currents passing into the primary coils is registered. At each revolution of the interrupter the string deviates sharply from a base line as the primary circuit is made; it hangs for an instant and returns sharply to its base line at the breaking of the circuit; these deflections are seen in Figs. 7 and 8. At each make and break of the right-hand circuit by the tapping key the string is deflected from or returns to the zero line; these movements are at once distinguished in the records by their irregular incidence and by the distance between the make and break of the circuit.†

The second string of the galvanometer (lower record in Fig. 7) is connected to a pair of non-polarisable contacts, and these are placed on the surface of the auricle at about 15 millimetres from and in line with the stimulating electrodes. The second string is used purely to record the responses of the auricular muscle and yields the usual sharp intrinsic deflection at each excitation of the muscle.

\* The secondary circuit is actually closed for about one-sixtieth of the cycle to exclude the make shock.

† It is to be noted that we have used in most experiments both make and break testing shocks, and include the readings of both in the majority of our tables. This has been necessary in some cases, and convenient in others, in building up a sufficient series of readings. The use of break shocks only as testing shocks would have so prolonged many of the experiments as to have made a comparison of early and late readings of the refractory period too precarious. Now it is known that, when shocks approaching threshold value are used, a stronger shock will give response at a slightly earlier period of the process of recovery than will a weaker shock (Samojloff,<sup>12</sup> Lucas<sup>9</sup> and Adrian<sup>1</sup>). It appears to be necessary, if the effects of make and break shocks are to be compared, that the make shocks should be well above threshold value. We have actually used them at a point 300 to 400 per cent. above threshold value. These percentages have been calculated by measuring and comparing the currents which it is necessary to pass through the primary coil when the induced shocks are at threshold value and at the strength used in our experiments. In our tables we mark the readings (*m* or *b*) according to the kind of stimulus which was used to obtain the reading. If there remains any possibility that break shocks yield responses at points too early for comparison with the no responses of make shocks, responses to the former may be cast out of our tables; thereby the values of the refractory periods are but little affected, and the tables are still more than sufficiently full to support adequately the conclusions at which we arrive. To be absolutely on the safe side, however, we have added to each group of measurements one or more experiments in which break testing shocks, and these only, have been employed. (See footnote to page 129.)



This method has the advantage that the shocks which control the rhythmic beats of the heart, and the shocks which test the refractory period, enter the muscle at precisely the same place. The measurements are made by means of the comparator, and confine themselves to the upper string shadow which records the electrical shocks. The measurement is taken from the second\* of two or more effective rhythmic break shocks (*rb*, Fig. 7) to the testing shock (*b*, Fig. 7) which falls after† it. These intervals are tabulated and a sufficient series is obtained to establish the limits of response

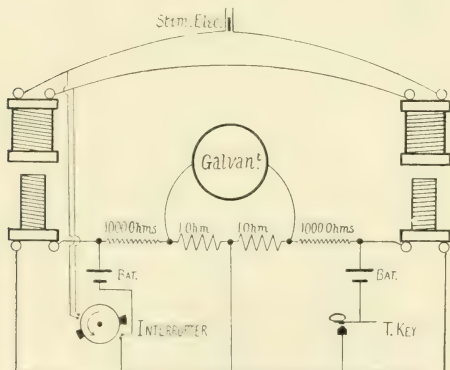


Fig. 1. A diagram of the apparatus used in testing the refractory period of the auricle.

and no response, responses being signalled by the second string. The object is to ascertain the shortest interval between two shocks, each of which yields a response and the longest interval between two shocks, the first of which alone yields a response. The intermediate value expresses the length of the refractory period.

\* It is a matter of moment that two effective rhythmic shocks should precede the test shock, for the refractory period is altered by the length of pause which precedes the systole whose refractory period is tested. That this pause should remain constant is a very necessary precaution.

† The measurement may not be made from a testing shock to the next rhythmic shock; for supposing both shocks to yield a response, the second follows a short period of rest, and the length of the refractory period measured would be subject to disturbance,

*Influence of the vagus upon the refractory period of auricular muscle.\**

In testing the refractory period of the auricle by this method, a group of plates is taken while the auricle is responding to rhythmic shocks and occasional testing shocks (Fig. 7). Inspection of the plates is in itself sufficient to determine the length of the refractory period within certain limits. If the rhythmic responses of the auricle are at a rate of 200 per minute then the length of each cycle is 0.3 of a second; the cycle corresponds to three tenths of a second; the tenths (or fifths) of a second are recorded on the plates as vertical lines. The testing shock falls after the preceding rhythmic shock at an interval which varies from 0.0 up to 0.3 of a second. The actual interval may be gauged by simple inspection of the plate with an error not exceeding plus or minus 0.02 of a second. If, on simple inspection of the plates, it is clear that the refractory period has a duration of let us say 0.1 (+ or - 0.02) of a second, then all intervals lying between these limits (*i.e.*, 0.08 on the one hand and 0.12 of a second on the other) are submitted to accurate measurement. A few more intervals are chosen and measured to build up the series, and all are then tabulated in order of length in decimal points of a second.† It is unnecessary finely to measure every interval on the plates while ensuring an accurate estimate of the refractory period. If the apparent refractory period lies at 0.1 of a second, it is only necessary to measure precisely, on the one hand, all intervals which have an apparent length of 0.12 of a second or *less*, and which are associated with response of the auricle; and, on the other hand, all intervals which have an apparent length of 0.08 of a second or *more* and which are associated with no response. The critical point lies at about 0.1 of a second, consequently it is unnecessary to measure precisely all the intervals, associated with response up to 0.3 of a second, or all the intervals down to zero, which are associated with no response. The method of selection used ensures accuracy, but it tends to over-emphasise somewhat the frequency of discrepancies, for all discrepancies become included in the tables.‡ In the tables "no response" is indicated by the readings which are in heavy type.

Table I includes readings obtained from the auricles of 9 dogs.§ and these are arranged under three headings. In the "control" columns are the intervals obtained when the auricle was responding to rhythmic shocks and occasional testing shocks at a single point. In other columns the intervals obtained in similar circumstances, but while the auricle was affected by vagal stimulation, are expressed (see Fig. 9). The intensity of vagal

\* A preliminary notice of these observations has been published in the Proc. physiol. Soc., December 18th, 1920.

† The readings given have no greater error than 0.001 of a second; usually the error is less than this figure.

‡ It may be taken for granted that responses always occurred when the intervals were greater than the largest shown in the tables and never occurred when the intervals were less than the smallest shown in the tables.

§ These dogs, like all the dogs on which the experiments recorded in this article were performed, were fully anaesthetised throughout with morphia, paraldehyde and ether.

stimulation used was such as to bring the ventricle to prolonged standstill; the right auricle and right vagus have been investigated exclusively. In other columns the intervals obtained in similar circumstances to the "control" intervals, but while the heart was saturated with atropine, are given.\* A horizontal line divides the readings of the table at the point which represents the length of the absolute refractory period. Thus in the vagal column of *Dog LP*, the intervals associated with response are 0.037, 0.048, 0.048 of a second, etc., while these associated with no response are 0.035, 0.026 of a second. The refractory period has a duration lying between 0.035 to 0.037 of a second. In the "control" column of *Dog LQ* there is an unimportant discrepancy, the interval 0.066 being associated with no response: in other instances the discrepancies are greater. We draw our line in each instance at the point where no response becomes constant, for reasons which will be discussed more fully when the meaning of these discrepancies is considered.

In the controls, and while the auricle is responding to rates approximating to 200 per minute,† the absolute refractory period is approximately 0.046, 0.061, 0.029, 0.047, 0.079, 0.041, 0.093, 0.075 and 0.118 of a second in the nine experiments.

Under vagal stimulation the refractory period in six of these experiments (the corresponding control readings are italicised above) is 0.036, 0.030, less than 0.020, 0.024, 0.014 and 0.028 of a second. The reduction is notable and constant. The average value is 0.025 of a second.

It is to be observed that the refractory period in the control observations is very variable, ranging from 0.029 to 0.118 of a second. This variation is due, in our view, to variation in the intensity with which the rhythmic shocks stimulate the vagal nerve endings in the auricle from animal to animal: for by the method employed, the refractory period is measured at the point at which these rhythmic shocks enter. The measurements of the refractory period expressed by the control columns do not express the natural refractory periods of the muscle, beating at 200 per minute: they express the refractory period of muscle in which the vagal nerve endings are in greater or lesser degree excited: and the comparison of measurements in the control observations and in those taken under vagal stimulation, do not fully display the influence of vagal stimulation upon the length of the refractory period. This local effect of rhythmic shocks upon the vagal nerve endings is proved by the measurements of the refractory period under atropine (see a previous article of this series<sup>5</sup>). In the atropinised auricle the refractory period measures 0.109, 0.127, 0.142, 0.124, 0.102,

\* Atropine sulphate in doses of from 0.01 to 0.02 of a gramme was used in dogs weighing 9 to 14 kilograms. The vagus nerve was strongly stimulated and the effect observed before and after the injection of atropine and after the completion of the series of observations under atropine in each instance.

† The rate of rhythmic stimulation chosen must be such that it will lie above the level of the spontaneously beating auricle in all the circumstances of the experiment.

TABLE I.  
*Refractory periods of auricle at point of rhythmic stimulation. Influence of vagus and atropine.*

Dog	L.P.		L.Q.		L.R.		L.S.	
Auricular rate.	235	235	220	210	204	204	208	205
	During vagal stimulation	Control	During vagal stimulation	Control	After atropine	Control	During vagal stimulation	Control
	0.068 <i>m</i> 0.007 <i>m</i> 0.054 <i>m</i> 0.051 <i>b</i> 0.068 <i>b</i> 0.048 <i>b</i> 0.048 <i>m</i> 0.037 <i>m</i>	0.006 <i>b</i> 0.078 <i>m</i> 0.069 <i>m</i> 0.068 <i>b</i> <b>0.063</b> <i>b</i> 0.059 <i>m</i> 0.048 <i>m</i>	0.084 <i>m</i> 0.084 <i>b</i> 0.083 <i>m</i> 0.062 <i>b</i> 0.058 <i>b</i> 0.048 <i>b</i> 0.046 <i>m</i> 0.045 <i>b</i> 0.042 <i>m</i> 0.038 <i>m</i>	0.105 <i>b</i> 0.096 <i>b</i> 0.094 <i>b</i> 0.073 <i>m</i> 0.071 <i>m</i> 0.071 <i>m</i> <b>0.066</b> <i>m</i> 0.064 <i>m</i> 0.063 <i>m</i>		0.087 <i>b</i> 0.072 <i>m</i> 0.043 <i>b</i> 0.041 <i>b</i> 0.040 <i>m</i> <b>0.032</b> <i>m</i> 0.030 <i>b</i>	0.065 <i>b</i> 0.052 <i>b</i> <b>0.035</b> <i>m</i> 0.033 <i>b</i> <b>0.033</b> <i>m</i> 0.033 <i>b</i> 0.030 <i>m</i> 0.028 <i>b</i> 0.025 <i>b</i>	0.079 <i>b</i> <b>0.068</b> <i>b</i> 0.064 <i>m</i> 0.059 <i>m</i> <b>0.053</b> <i>b</i> 0.050 <i>m</i>
Absolute refractory period	0.035 <i>m</i> <b>0.026</b> <i>m</i>	0.044 <i>m</i> 0.031 <i>m</i>	0.023 <i>m</i> <b>0.015</b> <i>m</i>	0.060 <i>m</i> 0.058 <i>m</i> 0.046 <i>m</i> 0.041 <i>b</i> 0.041 <i>b</i> 0.040 <i>b</i> 0.037 <i>b</i> 0.026 <i>m</i> 0.025 <i>m</i>	0.029 <i>b</i>	0.115 <i>m</i> <b>0.091</b> <i>m</i> 0.090 <i>m</i> 0.078 <i>b</i> 0.076 <i>m</i> <b>0.049</b> <i>b</i>	0.023 <i>m</i>	0.044 <i>m</i> 0.043 <i>b</i> 0.038 <i>b</i> 0.024 <i>m</i>

*Continuation of Table I.*

Dog	L.W.			L.X.			L.Y.			L.Z.			M.H.*		
	Control	After atropine		Control	After atropine		Control	After atropine		Control	After atropine		Control	After atropine	
Auricular rate	205	210	186	187	230	230	180	178	180	During vagal stim.	After atropine	180	205	204	207
Absolute refractory period			0.144 <i>b</i>										0.082		
			0.120 <i>m</i>										0.088		
			0.113 <i>m</i>										0.084		
			0.107 <i>b</i>										0.076		
			0.106 <i>b</i>										0.065		
			0.105 <i>b</i>										0.062		
			0.100 <i>m</i>										0.057		
			0.100 <i>m</i>										0.040		
			0.094 <i>m</i>				0.181 <i>b</i>						0.039		
			0.084 <i>m</i>				0.171 <i>m</i>						0.036		
			0.084 <i>b</i>				0.164 <i>m</i>						0.035		
			0.084 <i>b</i>				0.160 <i>b</i>						0.034		
			0.063 <i>m</i>				0.134 <i>b</i>						0.032		
			0.058 <i>b</i>				0.129 <i>b</i>						0.029		
			0.042 <i>b</i>				0.127						0.028		
			0.131 <i>b</i>				0.121 <i>m</i>						0.028		
			0.125 <i>m</i>				0.121 <i>m</i>						0.019		
			0.123 <i>b</i>				0.111 <i>m</i>						0.015		
			0.121 <i>m</i>				0.106 <i>m</i>						0.012		
			0.119 <i>m</i>				0.104 <i>m</i>						0.010		
			0.101 <i>m</i>				0.103 <i>m</i>						0.007		
			0.086 <i>b</i>				0.070 <i>b</i>						0.004		

\* Break shocks tabulated only.

0.139 and 0.132 of a second or, in the average 0.125 of a second. Under atropine the measured length of the refractory period becomes relatively constant, and such variation as is shown does not run hand in hand with the variations seen in the measured length of the period in the control experiments. Both the relatively low values of the controls, and the considerable variation seen in the control estimates, are evidently brought about by the local effect of the rhythmic shocks upon the branches of the vagus in the muscle.

The values obtained for the refractory period in the atropinised heart average 0.125 of a second. The full influence of the vagus is expressed by the figures 0.125 and 0.025 of a second. Under vagal stimulation the refractory period is reduced to one-fifth of its full value. The reduction from the *natural* value is probably less than this, for it may be supposed that normal vagal tone exerts some shortening influence in the unatropinised heart: there is reason for believing, however, that under the conditions of our experiments vagal tone is not very great (see page 124):\* in none of these experiments has the injection of atropine been followed by very appreciable quickening of the natural heart rhythm. It may be objected that the value 0.125 does not necessarily represent the refractory period of the heart beating naturally at 200 per minute, since the animals are deeply anæsthetised: this question of the effect of anæsthesia does not at present concern us: the object of these observations has been to obtain values for the refractory period which may be used in studying flutter and fibrillation, produced in the auricle under similar experimental conditions.

For the moment we are content to draw attention to the profound influence which the vagus exerts in reducing the refractory period under the conditions of our experiments: the period over which the auricular muscle is responsive is notably prolonged: in a cycle of 0.3 of a second, it is prolonged from 0.175 to 0.275 of a second. This action of the vagus, at first sight paradoxical, is in fact not so. Vagal stimulation exerts a profound influence upon the character of auricular contractions: they become conspicuously smaller, as may be seen by inspection of the chamber.† A depressing effect of vagal stimulation upon the contraction process, whereby both its strength and duration‡ are reduced, is to be assumed, and accounts for the phenomena witnessed.

\* That is almost always the case when the pericardium is open.

† A graphic illustration of this effect will be found in this *Journal*, 1913-14, v, 247, Fig. 11.

‡ Samojloff<sup>10</sup> noticed a conspicuous shortening of the *R-T* interval of the frog's ventricular electrogram under vagal stimulation, the rate of the ventricle being maintained at a constant point. Dale and Mines<sup>11</sup> recorded a similar change in the electrogram of the frog's auricle and ventricle, when the rate of the spontaneously beating heart was not greatly reduced by the vagal stimulation.

Raaflaub<sup>11</sup> measured the refracting period in four frogs' ventricles and in three other frogs' ventricles under vagal stimulation. His values are not very convincing, though Raaflaub concludes that the refractory period under vagal stimulation is very much shortened.

A special word is desirable upon the discrepancies displayed by this table. Some of these are inconspicuous: for example, the overlap (0.066) in the control series of *Dog LQ*; others are conspicuous and may scarcely be neglected, for example, the overlap (0.068) of the control series of *Dog LS*. It is to be remembered that a given series of observations may be spread over a period of perhaps 15 or 20 minutes, and that some variation in the actual refractory period may occur during the course of its measurement. But that is not a full explanation, for discrepancies which are not negligible are found from time to time, occurring within a few seconds of each other, and this is especially the case when the rate at which the auricle is driven is comparatively high.

*Influence of rate upon the refractory period.*

It is well known that the length of systole in cardiac muscle is influenced by the rate of beating, the systole becoming shorter as the rate increases. This relation between rate and length of systole was studied in considerable detail by Mines<sup>10</sup>, who worked with the frog's ventricle. It is probable, as Mines states, that the length of the ventricular electrogram and that of the refractory period are inter-related, and that the former may be taken, at all events approximately, as a measure of the latter.\* Mines, in discussing the length of the refractory period in its relations to rate, proceeded to apply further tests, which seemed to demonstrate that the refractory period shortens as the rate is raised. These tests will be referred to again at a later stage. For the moment it is sufficient to note that the relation of rate to refractory period has been demonstrated in the frog's ventricle.

In considering the bearing which length of the refractory period may have upon flutter and allied mechanisms in the mammalian auricle, this demonstration of Mines' upon the frog's ventricle is inadequate. We have considered it desirable to test the relation of rate to refractory period in the muscle concerned, namely, the mammalian auricle, and to place it, so far as possible, upon a quantitative basis. For this purpose we have used direct measurement.†

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\* According to Lucas' a second response of cardiac muscle does not occur until the electrogram of the first has subsided. That this is not always the case is shown by Samojloff's curves, and notably by those of Trendelenburg.<sup>9</sup> The relation between the end of the electrogram and the end of the refractory period is not yet precisely known. It is not known if such relation has an adequate degree of precision; such observations as we can consult suggest the contrary. It is probable that the relation varies a good deal in different circumstances, for instance, with the strength of stimulus (Samojloff) and with the rate of heart beat.

† To measure the length of the auricular electric complex, and to use this measurement in calculating the length of the refractory period of the auricular muscle beating at different rates has not appealed to us. Such a method, even if feasible, seems to us too indirect and is fraught with too many chances of gross error. Actually we believe that this method is not feasible in the case of the mammalian auricle.



*Direct measurement.* These measurements have been carried out by the method already described. In all our observations, which are given in Tables II and III, the heart has been fully atropinised to avoid any reduction of the refractory period consequent upon local stimulation of the vagus nerve endings. The lowest rate tested has been of necessity in excess of the spontaneous rate prevailing in the heart in the circumstances of each experiment.\*

The refractory periods as estimated from these tables are summed up in two diagrams (Figs. 2 and 3). As the auricular rate rises from between 120 and 200 to higher levels, the measured refractory period falls in value. At a rate of 100 it has an approximate value of 0.2 of a second;† at rates of 130 and 140 the value is approximately 0.15 or 0.17; as the rate rises higher the period falls further, until usually at about 290 per minute it lies between 0.08 and 0.11 of a second. This range of rates covers the *first phase* of the reaction.‡ In the *second phase* of the reaction, which lies usually from about 290 onwards, the decline in the measured value of the refractory period ceases; the curve tends to become flat, or, as is more customary, it actually rises. During this second phase also the values become often irregular. The second phase ends at variable rates, usually between 380 and 450 per minute.

In the *third phase* of advanced rate the heart fails to react to many of the impulses which reach it. At first an occasional response is missed; at a very slightly higher rate, a curious phasic disturbance becomes established, constituted by alternating periods of 1:1 and 2:1 response. The 2:1 response becomes permanently established if the rate is again advanced by some 20 or 30 beats per minute; permanent 2:1 response is usually established at rates of from about 400 to 480 per minute. The meaning of this 2:1 response is not in doubt: as the rate of stimulation is advanced the refractory period shortens, but it shortens less than does the length of the cycle; consequently the period of responsiveness diminishes. This gap of responsiveness becomes less and less until it vanishes altogether; when this happens the auricle fails to respond to alternate shocks. This phenomenon of half-response is well known, and has been described in some detail by Mines: but the events which lead up to it have received insufficient attention, and the phenomena do not appear to be quite the same, or to be related to equivalent ranges of rate, in the frog and mammals. The events which lead up to 2:1 response have been studied by us in detail, as they seem to possess a fundamental bearing upon the problem

\* These circumstances are such that the rates are high, higher than those prevailing in unanaesthetised dogs at rest; but this is for the most part immaterial in that it is particularly in relation to high rates of beating that knowledge of the refractory period is required in studying flutter.

† A single observation, not included in the tables. Rates as low as 100 are rarely displayed by the atropinised heart.

‡ The rate 290 is a mean critical value, sometimes the critical rate is lower, sometimes higher. Variations from animal to animal render precise references to rate difficult.







TABLE III.

*Refractory period related to heart rate in atropinised auricle.**(Tested by means of break shocks.)**Dog M.L.*

Auricular rate	122	150	185	230	240	278
Length of cycle	0.492	0.400	(v.sl.irreg.) 0.324	(irreg.) 0.260	(irreg.) 0.250	0.216
Transmission intervals	0.0187	0.0249	0.0296	0.0362	0.0432	
				0.147		Transient 2 : 1 response
				0.141		
				0.131		
				0.128		
				0.127	0.167	
				0.124	0.164	
				<b>0.123</b>	0.158	
				0.122	0.155	
	0.281			<b>0.118</b>	0.139	
	0.251			0.117	0.136	
	0.216	0.197		<b>0.113</b>	0.132	
	0.202	0.191	0.177	0.110	0.122	
	0.194	0.178	0.167	0.109	0.120	
	0.191	0.171	0.156	<b>0.108</b>	<b>0.119</b>	
	0.185	0.171	0.156	0.100	0.119	
	0.180	0.170	0.153	<b>0.097</b>	0.113	
	0.164	0.169	0.143	0.093	<b>0.111</b>	
	0.161	0.168	0.140	0.092	0.108	
	0.158	0.152	<b>0.138</b>	0.092	<b>0.107</b>	
	0.156	0.149	0.137	0.091	0.104	
Absolute R.P.	<b>0.148</b>	<b>0.149</b>	0.122	<b>0.089</b>	<b>0.087</b>	
	0.134	<b>0.146</b>	0.120	<b>0.080</b>	<b>0.080</b>	
	0.132	<b>0.139</b>	0.112	<b>0.075</b>	<b>0.070</b>	
	0.123	<b>0.134</b>	<b>0.109</b>	<b>0.074</b>	<b>0.064</b>	
	0.103	0.120	<b>0.109</b>	<b>0.062</b>	<b>0.056</b>	
	<b>0.098</b>	<b>0.109</b>	0.101	<b>0.061</b>	<b>0.049</b>	
	<b>0.094</b>	0.107	0.101	<b>0.056</b>		
	<b>0.086</b>		<b>0.088</b>	<b>0.049</b>		

*Dog M.B.*

Auricular rate	187	240	320	328	350	400	428
Length of cycle	0.320	0.250	(v.sl.irreg.) 0.187	(irreg.) 0.183	(irreg.) 0.171	0.150	0.280
						Transient 2 : 1 response	2 : 1 response
					0.154		
					0.144		
		0.177			0.144		
		0.177	0.164		<b>0.143</b>		0.189
		0.158	0.151		<b>0.140</b>		0.180
	0.172	0.152	0.142	0.166	0.138		0.174
	0.168	0.144	0.139	0.166	0.131		0.170
	0.155	0.142	<b>0.125</b>	0.132	<b>0.130</b>		0.168
	0.153	0.135	0.121	0.130	0.126		0.144
Absolute R.P.	<b>0.133</b>	<b>0.134</b>	<b>0.116</b>	<b>0.123</b>	<b>0.114</b>		<b>0.140</b>
	<b>0.131</b>	<b>0.126</b>	<b>0.113</b>	<b>0.099</b>	<b>0.111</b>		<b>0.140</b>
	<b>0.107</b>	<b>0.108</b>	<b>0.111</b>		<b>0.100</b>		<b>0.140</b>
			<b>0.107</b>		<b>0.098</b>		

of circus movements in the auricle. The relation of the three phases of the reaction are summed up in Table IV, in which other features, to be described, are also incorporated.

TABLE IV.

1st phase. (Rate up to 290.)	2nd phase. (Rates of 290 up to 380 or 450.)	3rd phase. (Rates of 380 to 480 and over.)
R.P. gradually reducing. Measured R.P. sharply defined, i.e. constant from cycle to cycle.	R.P. steady or rising. Measured R.P. irregular from cycle to cycle. Intrinsic deflections at first alternating and later irregular in amplitude and spacing. Transmission intervals lengthened and irregular.	R.P. occasionally or constantly longer than the inter-stimulus distance. Occasional missed response, transient 2:1 response and, finally, persistent 2:1 response.

In three instances we have measured the refractory period during the stage of persistent 2:1 response. We find that its length slightly exceeds the length of the inter-stimulus interval, as had been previously surmised. The overlap is trifling, amounting usually to less than 0.01 of a second. These observations are included in our tables, and may be summarised as follows:—

TABLE V.

Dog	LY.	LZ.	MB.
Rate of stimulation .. .. .	484	388	428
Rate of response .. .. .	242	194	214
Length of inter-stimulus interval (in sec.) .. ..	0.124	0.155	0.140
Length of refractory period .. .. .	0.124	between 0.155 and 0.168	0.142
Approximate length of R.P. at half the rate of stimulation ..	0.098	0.138	0.139

The value found for the refractory period in the stage of persistent 2:1 response does not depart very greatly from that found in the same auricles when the rate of stimulation is halved.\* These observations show that the length of the inter-stimulus interval, when the muscle has just entered the phase of *persistent* 2:1 response, is an approximate measure of the refractory period of the muscle beating at the half rate.

\* In the case of dog LY this correspondence is not close; such discrepancies are probably attributable to the considerable lapse of time between the two observations upon the refractory period.

Mines concluded that, if the rate of stimulation is gradually raised, until a response is first missed, the inter-stimulus interval measures the refractory period of the muscle beating at the full rate. That may be so for the frog's ventricle, but it does not hold for the dog's auricle. Readings so obtained are much too high. To emphasise this fact we tabulate the lengths of the inter-stimulus interval, at rates of stimulation at which transient 2 : 1 response first prevailed, and compare these with the refractory periods as measured while the heart responded to stimulation at approximately half these rates. If the relation expressed by Mines were to hold, the last values should be considerably higher than the first, for the lengths of the inter-stimulus intervals should approximate to the refractory period for the full and not the half rate of stimulation; actually they are in all instances lower (Table VI). The lack of the relation expected by Mines

TABLE VI.

<i>Dog</i>	<i>LX.</i>	<i>LY.</i>	<i>LZ.</i>	<i>MC.</i>	<i>MB.</i>	<i>MI.</i>
Transient 2 : 1 response Rate of stimulation	450	444	334	420	400	278
Inter-stimulus interval..	0.133	0.135	0.179	0.143	0.150	0.216
Half rate of stimulation Rate of stimulation	225	222	168	210	200	139
Approx. R.P.	0.115	0.102	0.150	0.128	0.143	0.150

brings us to discuss a peculiar feature of the curve of refractory period in the mammalian auricle, namely, the rise in its apparent value at advanced rates of stimulation. This apparent rise of the refractory period begins at a rate of about 290 to 310 per minute in the atropinised auricle. It is closely associated with three other events: (*a*) Frequent overlaps in the "response" and no "response" readings, from which the refractory period is gauged. (*b*) Variation in the amplitude, form and incidence of the intrinsic deflections, which correspond to the rhythmic responses. (*c*) A reduced rate of conduction in the auricular wall.

(*a*) *Overlap of readings.* These overlaps are shown in Tables II and III, and have been discussed briefly at an earlier stage. It is to be emphasised that they are independent of the strength of stimulation, as our tables clearly show; it is also to be repeated that they are not the result of gradual change of the refractory period during the course of observation. Overlaps are frequently to be found within a few cycles of each other. They express change in the length of the effective refractory period from cycle to cycle. We shall term that period of the cycle over which these overlaps are to be

encountered, the *partially refractory period*, and the phenomenon which underlies it, the state of *partial refractoriness*.<sup>\*</sup> The partially refractory period is found only at high rates of response. With solitary exceptions there are no overlaps<sup>†</sup> in the atropinised auricle beating at rates of 230 or 240 per minute and under. They appear between these rates and the rate of 290 and continue to be seen as the rate is further advanced up to the point where responses fail. Thus the range of rate over which these overlaps occur is very similar to the range over which the apparent refractory period rises.

(b) *Variation in the electrogram.* In a previous article<sup>7</sup> of this series, the variations in the form, amplitude and incidence of the intrinsic deflections displayed in the electrogram of the auricle, while the latter responds to high rates of stimulation, have been fully discussed. The tables of conduction rate there published show that these variations begin to appear at rates of 312, 373, 336, 361, 372, 362 and 450 per minute. These tables were compiled from the unatropinised auricle, and the rates of stimulation, necessary to produce variations in the curves, are in these circumstances somewhat higher. In the atropinised auricle variation is first seen at rates of 290, 242, 290, 395 and 320 (see Tables II and III). It continues to be seen as the rate of stimulation is advanced up to the point where half-response occurs.

(c) *Reduced conduction rate.* In the previous article to which we have referred, the association between variations in the form, etc., of the intrinsic deflections and apparent decline in the conduction rates of the muscle, was pointed out; the tables then published show the association to be an intimate one. So intimate is it that the appearance of irregular electrograms at a particular rate of response is, in our experience, an almost certain indication that raised transmission intervals may be demonstrated at this rate of response. We base this statement upon a large general experience of such curves both in the atropinised and unatropinised auricle.<sup>‡</sup> The rise in the transmission intervals is maintained and increases up to the point where responses to stimulation are missed.

To sum up, there is a phase of the curve of rising rate, in the atropinised auricle lying approximately between the lower values 250 or 290, and the higher values 400 to 450, during which four closely associated

\* In distinction to the term *relative refractoriness* which is used to designate that short period following the end of the absolute refractory period in the frog's heart (and also in somatic muscle), during which "response" or "no response" is governed by the strength of stimulation (Lucas, Adrian).

† Other than those slight overlaps which may be ascribed to error in measurement or slight changes in the absolute refractory period during the period of observation.

‡ We are able to indicate in an approximate manner the transmission intervals corresponding to the various auricular rates in Tables II and III. These intervals are the intervals between stimulus and intrinsic deflection, the point of stimulation and contact signalling the arrival of the excitation lying separated by from 15-20 millimetres in different experiments. The intervals include the interval of latency, however.

There are occasional exceptions to the statement, namely, at the earliest appearance of irregularity; conduction cannot always be shown to be depressed at such times, though it is almost certainly present.

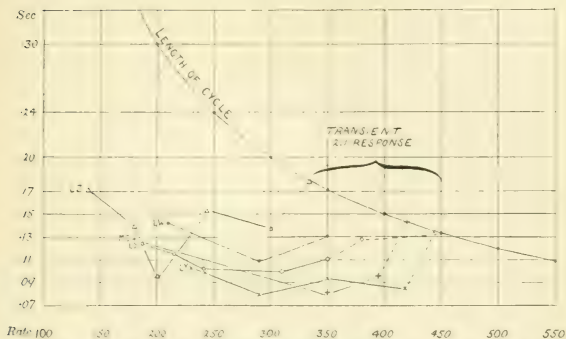


Fig. 2. A chart showing the relation between the absolute refractory period of the auricle and its rate of beating in five dogs.

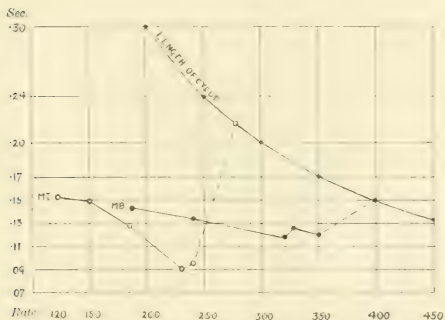


Fig. 3. A similar chart of the refractory period in relation to rate of beating in two further experiments.

phenomena are witnessed,\* namely, a rise in the apparent value of the absolute refractory period, the appearance of partial refractoriness, irregularity of the electrogram recording rhythmic responses, and an apparent decline of conduction rate. These four phenomena require a common explanation.

In a previous article of this series<sup>7</sup> variation in the electrogram and the increased and variable transmission intervals with which they consort were explained on the common basis of conduction disturbance, but at the time when that article was written the underlying factor in this apparent disturbance of conduction was not clear. The view favoured was that at high rates of stimulation small barriers to the progress of excitation waves through the auricular tissue became established, that these deflect the excitation wave and render its course sinuous, whereby the transmission intervals are prolonged. This view has been abundantly confirmed by our present observations, and we are now in a position to take the further step and to state that these barriers are constituted by muscle in which responsiveness is still incompletely recovered. We adopt the current conception of alternation, namely, alternate response or no response of individual muscle fibres of the heart, and agree with Mines, that occurring at high heart rates alternation of the fibres may be brought about by variation in the length of the refractory periods of these fibres; that, in the fibre, alternation is comparable to the state of 2:1 response in the muscle as a whole. Now alternation is the first form of irregularity exhibited by the electrogram as the rate is raised, but it soon gives place, as the rate is further raised, to more complex disturbances, which are to be assigned to similar causes. These disturbances shortly lead up to missed responses of the muscle as a whole. Let us suppose, then, that the first change which comes, as the rate advances, consists of alternating response of a percentage of the fibres. With each rhythmic shock a small proportion of the fibres fails to respond: these fibres respond to alternate shocks and beating at the half rate, their refractory periods are increased over those of the fibres which exhibit 1:1 response. The refractory period in a bundle of auricular fibres is no longer coterminous or nearly coterminous: the absolutely refractory may remain undisturbed, but to it must be added a period of partial refractoriness during which only a percentage of fibres can respond. If the percentage is a low one, this state of partial refractoriness will not display itself in measurements of the refractory period, since for every refractory fibre which the shock reaches there will be several or many responsive fibres, and these will yield response. But as more fibres enter the state of alternation the chances of obvious response during the period of partial refractoriness will diminish, until, eventually, shocks falling in this

\* In the preceding paragraphs figures for dogs *LZ* and *MI* have been neglected; they are exceptional in that the scale of rates is lower. Similar associations are to be noted in the tabulated statement of these observations: and, occurring at lower rates, emphasise all the more the close inter-relation of the phenomena discussed.



period will yield now a response and now none. In this manner we account for gross overlapping of the readings in our tables. The curve of absolutely refractory period is drawn in Fig. 4, and the vertical black bars represent this refractory period at different heart rates. The latter are represented as ending sharply and uniformly up to rates of 250 per minute. From the rate of 290 upwards a state of partial refractoriness is added and is represented by extending the length of the refractory period of certain fibres; they are extended upwards to a distance equivalent to the length of the refractory period at the corresponding half rate. As the rate increases, this upward extension is represented as becoming denser and approaching more and more closely the curve of the length of the cycles, until a rate is reached (450) when the line of relatively dense partial refractoriness meets the curve of the length of cycle. In other words, at this rate, the rhythmic shocks are entering muscle which is only very partially responsive. From the data of Tables II and III we are not justified in drawing these extensions higher, though we believe that the descending curve of cycle length is encountered at an earlier stage than is indicated in our diagram, and very possibly at the time when fibres first begin to alternate. We lack direct evidence that the refractory period is coterminous or otherwise in all the fibres at rates below 290. If the refractory period has a variable duration\* at relatively lower heart rates, and we see no reason to believe that this may not be the actual case, then the two curves would meet when fibre alternation begins and would overlap from this stage onwards. That they begin to overlap at the rate 450 is beyond question; that the first overlap comes earlier, and that at the rate 450 the overlap is a dense one, seems to us highly probable. It is, in fact, the hypothesis which we adopt, and we adopt it because it fully explains many of the phenomena which occur over the range of high rates. The existence of the partial refractory period is in no doubt: that it results from fibre alternation is consistent with the irregularity of the electrogram and with the overlapping readings of our tables: it also explains why 2:1 response first appears before it is expected. This 2:1 response is expected where the approaching curves of absolute refractory period and length of cycle are anticipated to meet: actually the 2:1 response comes much earlier than this anticipated point. The hypothesis explains why the curve of declining refractory period, as measured, becomes irregular and often ascends after rates of 290 are passed (see Fig. 4). Our hypothesis that the gap between the end of the absolute refractory period and the next stimulus is *bridged completely* by the partially refractory state at this rate, and those which exceed it, rests on further evidence.† The chief evidence is that of increased transmission intervals. At the rate 290 and sometimes before that rate is reached transmission rates in the auricle have declined. We

\* Not as a result of alternation, but as a result of idiosyncracies of the fibres.

† The interval left between the end of the partially refractory period in our diagram and the oncoming stimulus is actually but a small one (*i.e.*, 0.03 of a second, diminishing to zero); if our data are reliable it is necessary to assume the original variation in the length of fibre refractory period to amount to about 15 per cent. if the gap is to be bridged at a rate of 290.

shall bring forward what we regard as conclusive evidence that this decline is conditioned by the length of the partially refractory period a little later. For the moment it will facilitate argument if we assume our hypothesis; namely, that universal responsiveness of the fibres is lost at the rate of 290 or somewhat earlier. We shall assume for the moment that rhythmic impulses always enter partially refractory muscle when the rate exceeds 290 or thereabout. Entering muscle in this condition, all channels of passage are not open to the resultant excitation wave and, as the overlap becomes denser so the wave is deviated upon more and more sinuous courses: these deviations prolong its journey from point to point, and this raises the lengths of the transmission intervals. Thus, our hypothesis in its full form hangs chiefly upon our ability to demonstrate that the phenomena of alternation, more complex irregularity, and increased transmission intervals, are brought about by the maximal lengths of the refractory periods, and that the prolonged intervals and accompanying phenomena do not result from depressed conduction, using this word in the sense of fibre conduction. With this demonstration we now proceed.

*The effect of the vagus upon the rate at which excitation waves are transmitted through the auricular muscle.\**

Working in conjunction with Meakins and White,<sup>8</sup> some years ago, one of us investigated this question. The right and left appendix was investigated and also the tænia terminalis in its length. Both vagi were tested. These observations seemed to warrant the conclusion that vagal stimulation does not alter the rate at which the natural excitation waves are transmitted through the auricular muscle. They were necessarily complicated by lesser or greater changes in the rate of the auricular beat concurrent with the rise of vagal tone, though it seemed clear that this change in rate was often insufficient to invalidate our conclusion.

The possible effect of vagal stimulation upon the rate of transmission through the heart, and the possible production of block in the auricular walls, by this means, have so direct and important a bearing on many discussions relating to flutter and fibrillation of the auricle that we hesitated to rely entirely upon these earlier observations. Therefore, the subject has been re-investigated. The procedure adopted has been that described in an earlier article of this series.<sup>7</sup> The auricle is stimulated by means of rhythmic break shocks in line with two pairs of contacts resting on the muscle, and the interval between the arrival of successive excitation waves at the two pairs of contacts is measured. The method presents the advantage that, before and during vagal stimulation, the auricular rate is maintained at a constant level. The rate of stimulation used has been from about 200 to

\* A preliminary notice of these observations has been published in the *Proc. Physiol. Soc.*, December 18th, 1920

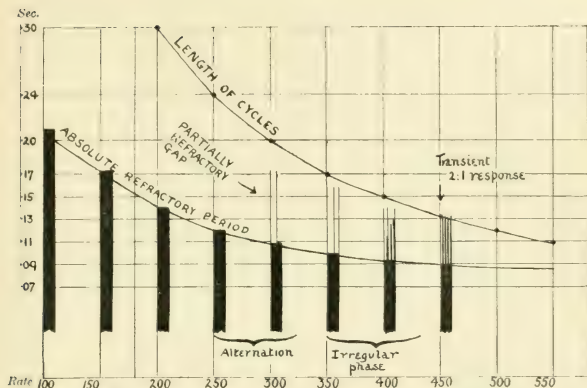


Fig. 4. A diagram illustrating the fall in the duration of the absolute refractory period as the rate of beating increases, and the relation of its ending to the end of the auricular cycle. To illustrate also the development of partial refractoriness and its relation to 2:1 response.

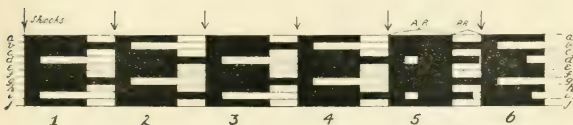


Fig. 5. A diagram of the refractory period of the auricle when the muscle is responding at a rate sufficiently advanced that it displays a partial refractory period (P.R.). A.R.=absolute refractory period.

300 per minute, and our results are given in Table VII. The body of the right auricle has been investigated in seven animals; the muscle fibres uniting the body of the auricle to the muscle of the superior vena cava have been tested in one animal, and those uniting the body to the muscle of the inferior cava have been tested in two animals.\* Vagal stimulation has been sufficiently strong to produce a high grade of block between auricle and ventricle, and thus to slow the ventricular rate profoundly. Both vagi have again been tested, though chief attention has been devoted to the right nerve. Although slight differences in the transmission intervals before and during vagal stimulation have been noticed, these differences have not amounted to more than one or at the most two thousandths of a second; the differences occur in both directions, are within or close to the margin of error,† and cannot be regarded as having any significance.

When the heart is driven rhythmically at rates of about 200 to 300 per minute, vagal stimulation has no effect upon the rate at which the excitation waves are propagated from contact to contact on the muscle, whether both these contacts lie on the body of the right auricle or whether one lies on the body and the other on superior or inferior vena cava. Taking these observations in conjunction with those previously described, we have no hesitation in concluding *that conductivity in the walls of the right auricle is uninfluenced by the vagus*. In using the term *conductivity* we use it in a restricted sense, and mean *the rate of conduction through individual muscle fibres*.‡

These observations upon the mammalian heart stand in apparent contrast to those of Gaskell upon the tortoise auricle.<sup>3</sup> Gaskell found that vagus stimulation may prevent the passage of waves of contraction across a bridge of muscle in the wall of the auricle, and interpreted this effect as a lowering of conduction power. Such an effect does not occur in the uninjured dog's auricle, and if we accept Gaskell's experiments as convincing on the one hand.§ and regard the dog's auricle as sufficiently representative of the mammalian auricle on the other, it would seem that in respect of conduction there is a fundamental difference between the action of the vagus upon the reptilian and mammalian auricular muscle. That the vagus acts upon the mammalian auricular muscle is clearly shown by the conspicuous decrease in the force with which it contracts while the nerve is being stimulated: the apparent

\* The last two regions were tested with a view to ascertaining if block could be induced at the sulcus terminalis.

† Minor changes from their usual form are not infrequently seen in the intrinsic deflections under vagus stimulation; this change renders comparative measurements a little less exact than they otherwise would be.

‡ In an earlier article<sup>1</sup> the term "rate of conduction" has been used in a broad sense, namely, as an equivalent for *the rate at which waves are transmitted through masses of fibres*. The distinction to which we now draw attention will be dealt with more fully a little later, and its importance will then become more apparent.

§ We feel that the experiments referred to should be repeated on the undamaged auricle of the tortoise and that increased transmission intervals under vagal stimulation should be observed, before it is finally concluded that the vagus depresses conductivity in the intact tortoise auricle.

TABLE VII.

*Effect of vagus on transmission rate in the auricle.*

Dog.	Muscle investigated.	Auricular rate.		Transmission interval.		Transmission rate.	
		Control	Vagus	Control	Vagus	Control	Vagus
<i>JM.</i>	Body of right auricle (9 mm. of muscle)	226	232	0.0105	0.0112	857	804
<i>JN.</i>	Body of right auricle (9 mm. of muscle)	252	254 251 259	0.0113	0.0136 0.0125 0.0114	796 720 789	662 789
<i>JO.</i>	Body of right auricle (9 mm. of muscle)	253	251 268	0.0134	0.0126 0.0137	672	714 657
<i>JQ.</i>	Body of right auricle (9 mm. of muscle)	263	268 212	0.0100	0.0102	900	882 811
<i>JR.</i>	Body of right auricle (9 mm. of muscle)	233	250 226	0.0117	0.0096	769	937 909
<i>JS.</i>	Body of right auricle (9 mm. of muscle)	188	196 198	0.0149	0.0139	604	648 634
<i>LF.</i>	Across upper tendon (16 mm. of muscle)	318	304	0.0282	0.0272	567	588
<i>LH.</i>	Body of right auricle (8 mm. of muscle)	259 290 267 282 279 278 284	259 286 279 286 276 274 282	0.0070 0.0069 0.0069 0.0065 0.0064 0.0078 0.0071	0.0063 0.0072 0.0070 0.0067 0.0079 0.0092 0.0079	1,143 1,159 1,169 1,231 1,250 1,026 1,127	1,270 1,111 1,143 1,194 1,013 870 1,013
	Across upper tendon (16 mm. of muscle)	284 280 298 294 294 309	292 286 296 294 292 292*	0.0252 0.0257 0.0233 0.0239 0.0257 0.0235	0.0252 0.0237 0.0254 0.0233 0.0218 0.0217	635 623 687 689 623 681	635 675 630 687 734 737
<i>LN.</i>	Across lower tendon (16 mm. of muscle)	242 250 250	280 252 250	0.0067 0.0055 0.0083	0.0072 0.0051 0.0068	In these observations the excitation waves were not passing in the direct line of the contacts. (Transmission rates are omitted consequently.)	
<i>LQ.</i>	Across lower tendon (16 mm. of muscle)	267 261	262 262	0.0044 0.0058	0.0024 0.0043		

\* Variation in amplitude of intrinsic deflections abolished.

difference of the vagus upon conduction would be qualitative therefore and not quantitative. We suggest that the difference, if it really exists, may have arisen during the phylogenetic development of the tissue; the muscle of the cold blooded-auricle is less developed, the auricle in its structure approaches more nearly to the original primitive tube. A slowing of the contraction wave in its course over a primitive muscular tube, constituting a pump, would have obvious advantages when that pump is meeting serious resistance; a similar slowing of the wave over the highly developed auricle of the mammal presents no obvious advantage. The mammalian auricle has developed so that the wave may be carried quickly to all parts of it, and so that contraction in its different parts may be almost simultaneous. In its phylogenetic development, the auricle may have thrown off this element of vagal control which is no longer serviceable to its work, while it has remained under that element of control, namely, control over the force of its contraction, which still exerts a useful influence.

TABLE VIII.  
*Vagus on transmission intervals. Auricle responding at high speeds.*

Dog.	Muscle investigated.	Auricular rates.		Transmission intervals in sec.		Transmission rate in mm. p. sec.	
		Control	R.vagus	Control	R.vagus	Control	R. vagus
L F.	Body of right auricle (8 millimetres)		327		0.0139		576
		380	371	0.0151	0.0127	530	630
		414		0.0163		491	
		443	433	0.0208	0.0129	385	620
L G.	Body of right auricle (8 millimetres)	351	346	0.0105	0.0111	762	721
	Across lower tænia (16 millimetres)	391	386*	0.0232	0.0143	690	1,118
		422	432*	0.0184	0.0128	869	1,250

\* Variation of the intrinsic deflections abolished.

Our experiments also show how important it is that, in considering the functions of the vagus, an effect upon the tissue in one part of the heart should not be regarded as sufficient evidence of a similar action upon tissue in another part. The vagus exerts a powerful influence upon the tissue uniting auricle and ventricle; it produces block of high grade in this situation; in the wall of the auricle itself it has no such effect. The fallacy of arguing from the first situation to the last is clearly displayed.

*Effect when auricles are responding to high rates of stimulation.* We have seen that the vagus exerts no influence upon the transmission intervals when the auricle is responding at rates up to 300 per minute; it is upon this observation that we base our conclusion that the vagus has no control over fibre conduction in the auricle.

When the auricle is driven at higher speeds, namely, from 300 or 350 per minute and upwards, the transmission intervals widen out in response to these



rates; sometimes the delay in transmission from point to point is displayed equally in successive cycles: more frequently it is unequal from cycle to cycle, not infrequently the intervals alternate in length; it is the average interval which is raised in value. We have discussed the meaning of these widened intervals, and have attributed them, not to depressed fibre conduction, but to the sinuous course of the excitation wave in its progress from point to point, attributing the sinuosity of course to barriers of refractory fibres which deflect the waves from their shortest paths. Now, if this explanation is the correct one, any influence such as vagal stimulation, which will lower the refractory period of the muscle, should remove these barriers, and raise the rate at which excitation waves are transmitted from point to point. This is precisely what is found to occur. If the rate of stimulation is driven sufficiently high to produce lengthened transmission intervals, *i.e.*, to rates of 300, 350 or over in the unatropinised auricle, then the factor which is responsible for delayed transmission in these circumstances is removed by vagal stimulation. It is not simply a question of the high rate of stimulation producing one change and the vagus producing an opposing

TABLE IX.

*Vagus on transmission intervals Auricle responding at high speeds.*

Dog.	Muscle investigated.	Auricular rate.		Stimulus to intrinsic interval in sec.		Intrinsic to intrinsic interval in sec.	
		Control	R.vagus	Control	R.vagus	Control	R.vagus
M D.	Body of right auricle (8 millimetres)	258	258			0-0070	0-0074
		312	312			0-0062	0-0066
		375	375*			0-0072	0-0071
		382	395*			0-0068	0-0065
		407	404*			0-0093	0-0076
		422	409†			0-0104	0-0070
M E.	Body of right auricle (8 millimetres)	233	230	0-0454	0-0459	0-0110	0-0104
		275	267	0-0441	0-0463	0-0114	0-0136
		318	311	0-0441	0-0444	0-0116	0-0111
		360‡	350	0-0421	0-0445	0-0110	0-0107
M F.	Body of right auricle (8 millimetres)	225	225	0-0326	0-0319	0-0070	0-0076
		266	262	0-0317	0-0298	0-0077	0-0074
		332	323	0-0277	0-0282	0-0083	0-0081
		386	390	0-0274	0-0263	0-0091	0-0090
		426	426	0-0289	0-0246	0-0110	0-0099
		509	510†	0-0365	0-0315	0-0123	0-0076
M G.	Body of right auricle (8 millimetres)	257		0-0618		0-0059	
		509	492*	0-0701	0-0636	0-0213	0-0061
M K.	Rt. appendix (8 millimetres)	200		0-0337		0-0105	
		422	422‡	0-0445	0-0343	0-0100§	0-0099

\* Variations less.

† Variation in amplitude of intrinsic deflections abolished.

‡ Rate driven insufficiently high to produce slow transmission.

§ For a reason, which will be described at a later stage, in this instance the stimulus to intrinsic interval is alone increased.

change; the vagus is without influence until the prolongation has been induced. As the only known action of the vagus, which is relevant, consists in a reduction of the refractory period, it is to this influence, and to this only, that its action can be ascribed. The action of the vagus upon the widened transmission intervals in the auricle is opposite in direction to that which it exerts at the A-V ring.\* A tendency for the vagus to reduce the transmission intervals is shown in several instances in Table VII: it is very clearly displayed by Table VIII. In general, the higher the rate of rhythmic stimulation the more conspicuous is the reduction.

Not only is there the reduction, but if vagal stimulation is prolonged until its full influence is exerted on the auricle, the transmission intervals can be shown to fall to those which prevail when the same auricle is responding to lower rates of rhythmic stimulation. In support of this statement we publish Table IX, in which the intervals at high and low rates of response are compared.† Whenever, as a result of a high rate of response, the intervals are increased, vagal stimulation reduces them to their original levels. This observation clearly demonstrates that widened transmission intervals in the auricle, responding to high rates of stimulation, are not due to change in fibre conduction but to the relation between the length of the cycle and the duration of the refractory period. Precisely how is the widened transmission interval engendered? At high rates of stimulation the shocks fall during the partially refractory phases of the preceding responses. The shocks fall upon muscle fibres, some of which have recovered, some of which have not; the former respond, and waves of excitation are propagated; the waves are propagated along courses upon which refractory fibres stand; these deflect the waves, prolonging their courses, and thus delay transmission from point to point. The higher the rate of stimulation the more numerous will the refractory fibres become; the more numerous the refractory fibres the more sinuous the course of the waves and the greater the delay. The more massed are the refractory fibres in a particular locality the greater will be the magnitude of the deviations which they cause. If the fibres which respond are concentrated for the most part in one series of cycles and those which fail are concentrated for the most part in the alternate series of cycles, then alternation in the length of the transmission intervals will follow. If the concentration is variable, rather than alternating, from cycle to cycle, the length of the intervals will vary rather than alternate. Thus, our hypothesis brings us quickly to a sufficient explanation of the phenomena actually observed.

\* The degree of auriculo ventricular block is increased by vagal stimulation.

† In this table we are able to introduce for most animals not only the transmission interval between proximal and distal contacts (inter-intrinsic intervals) but also the time intervals between the stimulus and intrinsic deflection of the proximal contacts. The last interval includes not only the transmission interval between point stimulated and proximal contact, but also such interval of latency of response as may exist. The last is perhaps a defect, but when waves of excitation take sinuous courses, the stimulus to intrinsic interval sometimes presents a distinct advantage, to which we shall refer at a later stage.



*Variations in the amplitude of intrinsic deflections.*

The observation which first suggests alternating response of individual fibres at high rates of stimulation is alternation in the heights of the intrinsic deflections, which would thereby be explained adequately. This phenomena, as has been shown in a previous article,<sup>7</sup> is associated with alternation in the lengths of the transmission intervals. This simple disturbance rarely retains purity of form as the rate is raised: it passes into more complex irregularities of amplitude, and when this change comes the transmission intervals show similar variation from cycle to cycle. The heights of the deflections are irregular,\* the transmission intervals are in the average raised. Vagus stimulation not only reduces the average interval to its original value, while rendering the intervals uniform, but it abolishes the irregularity in the amplitude of intrinsic deflections. A curve which shows conspicuous alternation, or more gross variation in the heights of its deflections, becomes steady under the influence of this nerve. Instances of this effect are noted in Tables VII, VIII and IX. In Fig. 10 the upper record is that of the shocks of stimulation, the lower record is an electrogram of the auricular response. The variation in the heights of the deflections is conspicuous over the first two thirds of the curve: under vagal stimulation it diminishes, eventually to vanish as the record ends. This type of curve is the rule: the irregularity may even increase a little at first: but this increase, if it occurs, is very temporary; when the vagus influence is maintained and allowed to exert its full power, the deflections, usually diminishing in size, become of constant amplitude. In less typical records the reaction is more sudden, as in Fig. 11, and the deflections become uniform within less than a second of the onset of vagal stimulation. As this record shows, they do not always decrease in height (see Fig. 10), as they become regular in form and amplitude. Slight but distinct irregularities in the incidence of the deflections result from the associated variations in transmission intervals, and these vanish also when the intervals become reduced to uniformity under the influence of the vagus. The effect of vagal stimulation upon the deflections of the curve, whereby alternation and more complex variation is abolished, shows again that these are brought about by the relation of the refractory period to the length of the cycle.†

In the light of these observations we conclude that the first appearance of partial refractoriness is due to "response" and "no response" of certain

\* These are wholly independent of respiration. Our records have been taken always during suspended respiration.

† Variation in the amplitude of the deflections may be explained in one or two ways. Thus, alternation in amplitude may be anticipated if a greater number of fibres become excited beneath the recording contacts at alternate cycles. It would also be explained if at alternate cycles the contacts were struck at a slightly different angle, consequent upon deviation of alternate waves from the straight path. No doubt this factor sometimes contributes, but the shorter stimulus to intrinsic interval does not always correspond to the highest deflection, as would be expected were this the only factor concerned in the variation. There are occasions in which alternation in amplitude, but not in intervals, is seen, and vice versa.

fibres to alternate shocks. In explaining the density of partial refractoriness, however, simple alternation may not suffice perhaps. The process is very probably more complex.

In Fig. 5 a fragment of auricular tissue is supposed to consist of 10 fibres *a* to *j* and, for several cycles (1-4), four fibres are represented as alternating. Fibres *b* and *g* are shown as responding in cycles 1 and 3 and failing to respond, owing to the length of their refractory periods, in cycles 2 and 4. Similarly, fibres *d* and *i* respond in cycles 2 and 4 and fail to respond in cycle 1 and 3. In a theory which allows no more than simple alternation, this process, once established, must be permanent, and further change can come only if more fibres begin to alternate. It is to be noted that even in the early stage diagrammatised, some fibres become responsive very shortly after the rhythmic shock reaches them: these are the fibres which fail to respond to the shock, being already in the refractory state. A testing shock, falling very shortly after the rhythmic shock, should find these fibres responsive. It may be asked why evidence of such response is not obtained, and why the end of the absolute refractory period is measured at a time when the bulk of fibres are thought to become responsive? A record is not to be expected from the response of single fibres, buried in a mass of refractory fibres, since no excitation wave would propagate itself to the recording contacts. But if it were supposed that the number of alternating fibres increased until, at certain cycles, half failed to respond and shortly became again responsive, then occasional evidence of response to very early testing shocks would seem inevitable. Yet it does not occur. For this and other reasons, simple alternation appears inadequate as an explanation. It is to be remembered that we are dealing with a syncytium of muscle fibres, and that such a network as exists provides many channels of re-entry. If certain fibres, which do not respond to the rhythmic shock, become responsive at a very slightly later interval these are surrounded and joined to fibres which do respond and through which excitation waves are carried. It seems possible, if not probable, that the fibres, which become responsive soon after the shock enters the muscle, may respond, not to the shock, but to excitation waves entering a little later from adjoining fibres. This is diagrammatically represented in cycle 5 of the same figure. Allow that the two factors come into play, namely, fibre alternation on the one hand and re-entry from neighbouring fibres on the other, and a condition will be brought about, compatible, so it seems to us, with all the phenomena with which we are dealing. The end of the refractory period in the muscle fragment as a whole will lack uniformity. For a considerable period all the fibres will be refractory, the absolute refractory period being represented by the period marked *AR* in the diagram: succeeding this will come a period of partial refractoriness (*PR*) of variable density, and lasting up to the next shock. At the actual time of the shock this density will not be so great that the muscle will fail to respond, but in its early phases it may be sufficiently dense to give no response. In such circumstances the measure of the absolute refractory period for that

cycle will be prolonged. But the grouping from cycle to cycle will vary, and testing shocks falling at the same phase of different cycles will yield contrary replies. Thus we explain the overlaps in the readings of our tables (Tables II and III). We desire to lay no emphasis upon the detailed construction of this diagram, realising that such diagrams often tend to convey more than is intended. It serves as an illustration, and may help to convey an idea of our conception. Some such explanation seems to us to be necessary to explain the curious reactions of the auricle responding to high rates of stimulation. Further light is thrown upon the condition of the muscle by studying in detail the transition from 1 : 1 to 2 : 1 and from 2 : 1 to 1 : 1 response in the auricle as a whole.

*Transition from 1 : 1 to 2 : 1 response.*

It has been stated that when the rate of stimulation is sufficiently raised the auricle eventually fails to respond. In the mammalian auricle this happens at much the same rate, whether the rate is raised gradually or in steps. The first sign is failure to respond to a single shock, and it is a failure of the whole auricle to respond.\* If the rate of stimulation, at which the first response is missed, is maintained, the auricle continues to respond to most of the shocks, but fails occasionally. There is no abrupt passage from continued 1 : 1 to continued 2 : 1 response. As the rate is raised further the 2 : 1 responses become more frequent, but they are intimately mixed with 1 : 1 responses only on rare occasions : the character of response almost always becomes phasic (see Fig. 12), short periods of 1 : 1 and 2 : 1 response alternating. If the rate is higher, the 2 : 1 periods are the longer ; if the rate is lower, the 1 : 1 periods are the longer. If the rate is maintained, this phasic change from 1 : 1 to 2 : 1 response and back again is maintained for long periods. Now, if we regard the refractory periods as coterminous in all the fibres of the muscle stimulated, these events could not occur. The response of the muscle which succeeds the first missed response has, by virtue of the greater period of rest preceding it, a longer refractory period.† It would be anticipated that this lengthening of the refractory period would

\* We have not seen failure of a part of the auricle to respond, and do not think such failure is ever spread over a mass of muscle sufficient to be recognised by the eye. On one occasion, when we thought we witnessed it, an electrical record from the muscle which appeared to beat at half-rate proved it to be alternating, the electrical responses being at the full rate.

† This has been shown by Mines<sup>10</sup> for the frog's ventricle in the following way. While the heart is responding to rhythmic shocks at a maximal rate, a single shock is intermitted ; this intermission is followed by a condition of permanent 2 : 1 response. In the mammalian auricle the same phenomenon is witnessed when two shocks are intermitted, but the period of 2 : 1 response which follows is always very fleeting. In testing the refractory period of the auricle at different rates of stimulation, it often happens that the testing shocks fall a little distance before the rhythmic shock, and the latter finds the muscle refractory. An unusual pause now follows, and it is often noticeable that the refractory period of the succeeding response to a rhythmic shock is unusually long. The introduction of such readings is, of course, avoided in our tables, the rule being that the testing shock is to be preceded by two or more effective rhythmic shocks.

TABLE X.  
*Spontaneous change from 2:1 response to 1:1 response, and vice versa, during high rates of stimulation of the auricle*  
 (1) Stimulus and intrinsic (1) (proximal contacts).  
 (2) Intrinsic (1) (proximal contacts) and intrinsic (2) (distal contacts).

Dog Rate of Stimulation	MG (Record 17), 520 per min.		MG (Record 20), 508 per min.		MF (Record 25), 475 per min.		MJ (Record 9), 440 per min.		MJ (Record 10), 440 per min.	
	Stimulus to Intrin. (1)	Intrin. (2)	Stimulus to Intrin. (1)	Intrin. (2)	Stimulus to Intrin. (1)	Intrin. (2)	Stimulus to Intrin. (1)	Intrin. (2)	Stimulus to Intrin. (1)	Intrin. (2)
2:1 response	0-0597 0-0586 0-0614 0-0562	0-0076 0-0086 0-0085 0-0077	0-0602 0-0609 0-0611	0-0077 0-0086 0-0083	0-0400 0-0374 0-0377	0-0109 0-0101 0-0115	0-0364 0-0354	0-0051 0-0055	0-0358 0-0348 0-0346 0-0340	0-0048 0-0045 0-0045 0-0044
1:1 response	0-0727 0-0596 0-0632 0-0602 0-0609 0-0619 0-0639 0-0613 0-0620 0-0622 0-0639 0-0647 0-0796	0-0113 0-0112 0-0114 0-0111 0-0086 0-0087 0-0102 0-0109 0-0087 0-0112 0-0087 0-0095 0-0154	0-0755 0-0614 0-0683 0-0662 0-0662 0-0614 0-0635 0-0625 0-0641 0-0652 0-0669 0-0662 0-0711 0-0666 0-0673 0-0626 0-0650 0-0678 0-0662 0-0686	0-0155 0-0165 0-0120 0-0119 0-0095 0-0095 0-0159 0-0146 0-0145 0-0129 0-0126 0-0138 0-0139 0-0160 0-0136 0-0147 0-0144 0-0148 0-0142 0-0163 0-0148	0-0514 0-0443 0-0436 0-0350 0-0438 0-0420 0-0426 0-0377 0-0428 0-0453 0-0446 0-0414 0-0458 0-0386	0-0151 0-0104 0-0119 0-0107 0-0099 0-0107 0-0110 0-0093 0-0112 0-0100 0-0117 0-0120 0-0109 0-0126	0-0478 0-0378 0-0415 0-0390 0-0066 0-0437 0-0410	0-0082 0-0067 0-0059 0-0066 0-0074	0-0465 0-0374 0-0408 0-0410 0-0463 0-0450 0-0488 0-0463	0-0079 0-0071 0-0073 0-0083 0-0097 0-0061 0-0082 0-0168
2:1 response	0-0571 0-0557 0-0544 0-0542 0-0542	0-0083 0-0083 0-0085 0-0080 0-0089	0-0565 0-0078 0-0606 0-0638	0-0059 0-0078 0-0080 0-0085	0-0384 0-0361 0-0376	0-0113 0-0107 0-0098	0-0349 0-0356	0-0041 0-0040	0-0368 0-0346 0-0362	0-0053 0-0046 0-0053

TABLE XI.

Spontaneous change from 2:1 response to 1:1 response, and vice versa, during high rates of stimulation of the atropinised auricle.

Dog Rate of Stimulation	ME (Record 28), 415 per min.				MF (Record 41), 438 per min.				MF (Record 42), 432 per min.				MJ (Record 36), 375 per min.			
	Stimulus to Intrin. (1)	Intrin. (1) to Intrin. (2)	Stimulus to Intrin. (1)	Intrin. (1) to Intrin. (2)	Stimulus to Intrin. (1)	Intrin. (1) to Intrin. (2)	Stimulus to Intrin. (1)	Intrin. (1) to Intrin. (2)	Stimulus to Intrin. (1)	Intrin. (1) to Intrin. (2)	Stimulus to Intrin. (1)	Intrin. (1) to Intrin. (2)	Stimulus to Intrin. (1)	Intrin. (1) to Intrin. (2)	Stimulus to Intrin. (1)	Intrin. (1) to Intrin. (2)
2:1 response	0.0163	0.0136					0.0419	0.0109	0.0395	0.0116						
	0.0171	0.0124			0.0139	0.0098	0.0415	0.0098	0.0405	0.0108						
	0.0185	0.0114			0.0120	0.0097	0.0414	0.0097	0.0405	0.0100						
					0.0193	0.0098	0.0405	0.0098	0.0405	0.0104			0.0413	0.0081		
1:1 response	0.0384	0.0100	0.0576	0.0113	0.0113	0.0138	0.0543	0.0138	0.0522	0.0142	0.0460	0.0085				
	0.0234	0.0127	0.0467	0.0119	0.0119	0.0120	0.0468	0.0120	0.0422	0.0134	0.0428	0.0078				
	0.0301	0.0134	0.0447	0.0139	0.0139	0.0123	0.0446	0.0123	0.0453	0.0130	0.0455	0.0096				
	0.0202	0.0134	0.0354	0.0129	0.0129	0.0138	0.0446	0.0138	0.0316	0.0158	0.0425	0.0085				
	<b>0.0410</b>	0.0121	0.0339	0.0100	0.0100	0.0154	0.0435	0.0154	0.0316	0.0131	0.0472	0.0088				
	0.0236	<b>0.0135</b>	0.0312	0.0100	0.0100	0.0134	0.0324	0.0134	0.0420	0.0135	0.0439	0.0074				
	<b>0.0326</b>	0.0132	0.0299	0.0126	0.0126	0.0145	0.0416	0.0145	0.0436	0.0160	0.0500	0.0088				
	0.0207	0.0132	0.0292	0.0109	0.0109	0.0155	0.0427	0.0155	0.0433	0.0144	0.0425	0.0081				
	<b>0.0326</b>	0.0121	0.0328	0.0123	0.0123	0.0348	0.0427	0.0348	0.0438	0.0155	0.0478	0.0092				
	0.0200	0.0121	0.0286	0.0120	0.0120	0.0158	0.0410	0.0158	0.0422	0.0166	0.0443	0.0070				
	<b>0.0315</b>	0.0161	0.0299	0.0133	0.0133	0.0321	0.0431	0.0321	0.0416		0.0465	0.0084				
	0.0216	<b>0.0161</b>	0.0286	0.0116	0.0116	0.0164	0.0443	0.0164			0.0443					
	<b>0.0332</b>	0.0137	0.0299	0.0126	0.0126	0.0172	0.0858	0.0172								
	0.0198	<b>0.0180</b>	0.0317	0.0109	0.0109											
	<b>0.0309</b>	0.0159	0.0309	0.0133	0.0133											
	0.0196	<b>0.0180</b>	0.0312	0.0116	0.0116											
(Cont. Inaug.)																
2:1 response			0.0174	0.0150	0.0150	0.0109	0.0467	0.0109	0.0409	0.0139	0.0398	0.0048				
			0.0152	0.0135	0.0135	0.0102	0.0415	0.0102	0.0405	0.0100						
						0.0117	0.0422	0.0117	0.0403	0.0108						

render the next shock abortive and that a condition of 2 : 1 response, by a repetition of this process, would become stabilised. Actually this does not occur.

Although, in the mammalian auricle, there is evidence to show that a single 2 : 1 period tends to be followed by a second of the same kind, and that a single 1 : 1 period tends to be followed by a second of the same kind, yet stability of the 2 : 1 response is never reached until the rate of stimulation is raised a good deal beyond the point at which the first response is missed. The form of response in the dog's auricle fluctuates because the effective refractory period fluctuates from cycle to cycle; the partially refractory period varies in duration and density from cycle to cycle; hence a stable 2 : 1 response is not seen until the period of partial refractoriness is prolonged so considerably beyond the instants at which the rhythmic shocks fall, that when these enter the muscle they always find the majority of the fibres refractory.

The actual events at the passage of a condition of 1 : 1 into 2 : 1 or 2 : 1 into 1 : 1 response are subject to a good deal of variation. We have studied them in a large number of curves, and the tabulated measurements of Tables X and XI are sufficient illustrations. Rhythmic shocks are thrown into the tip of the right appendix and two pairs of contacts are laid in line with the stimulating electrodes, upon the chief muscle band which runs from the base to the tip of the appendix, or upon the body of the auricle. The measurements used are, firstly, the interval between the instant of stimulation\* and the appearance of the excitation wave at the proximal contacts (this is stated in our tables as the stimulus-intrinsic interval); and, secondly, the interval separating the arrival of the excitation wave at the two pairs of contacts (this is stated in our tables as the intrinsic-intrinsic interval). The first interval (*S-I*) measures the time taken for the excitation wave to travel from the point of stimulation to the proximal contacts, a distance which has varied in our experiments between about 10 and 30 millimetres†: the second interval measures the time taken for the excitation wave to pass from proximal to distal contacts (*I-I*), a distance which has been uniformly 8 millimetres. Two tables are given, one for the atropinised, the other for the non-atropinised auricle. The chief differences shown between the two is that a higher rate of stimulation is required to produce transient 2 : 1 response in the latter (see Table XVIII).

During the phases of 2 : 1 response the intrinsic deflections are uniform in amplitude, and the transmission intervals (*S-I* and *I-I*) are uniform and relatively short: during the phases of 1 : 1 response the intrinsic deflections vary much in amplitude and sometimes a good deal in form; the transmission intervals vary and are in the average much prolonged.

\* This is usually signalled by escape into the lead from the proximal contacts, as in Fig. 12; otherwise it is signalled by means of a third string.

† It also included the period of latency of response, which, however, experience shows us, may be neglected in these experiments.



We now call attention again to our conclusion that prolongation of the transmission intervals, when the auricle is responding at high rates, is due to the sinuous path taken by the excitation wave. The deviations from the natural course may be small and numerous, or the deviation may be considerable. The swerve may be so great that the excitation wave, propagated from the point stimulated, strikes the recording contacts very obliquely (an extreme instance of this is shown diagrammatically in Fig. 1 of the third article of this series<sup>7</sup>). Swerve of this extent is sufficiently frequent to complicate the readings obtained, for, when the recording contacts are struck obliquely, the transmission interval ( $I-I$ ) is thereby reduced and an exact estimate of the transmission rate is not obtained from the reading. Evidence of decreased transmission rate is always obtained by measurement of the  $S-I$  intervals; it is not always made clear, though it usually is, by measurement of the  $I-I$  intervals, and this is especially the case when the rate of stimulation is so high that the swerve is conspicuous. Of swerve and its effects upon the transmission intervals, hitherto strongly suspected, we now have conclusive evidence. Consider, for example, the readings of the accompanying short table of measurements from a period of 1:1 response at high rate (Table XII). Both the  $S-I$  and  $I-I$  intervals are

TABLE XII.

*Alternating transmission intervals.**(Dog MK. Record 3. Rhythmic stimulation, rate 422 per minute, 1:1 response.)*

Stimulus to intrinsic interval in secs.	Intrinsic to intrinsic interval in secs.
0.0426	<b>0.0110</b>
<b>0.0443</b>	0.0087
0.0422	<b>0.0103</b>
<b>0.0460</b>	0.0094
0.0432	<b>0.0110</b>
<b>0.0485</b>	0.0097

alternating; but there is this curious relation, the long  $S-I$  interval corresponds to the short  $I-I$  interval, the short  $S-I$  interval to the long  $I-I$  interval. This arrangement can have but one meaning; an  $S-I$  interval is unusually long because the swerve of the excitation wave, in travelling from point of stimulation to contact, is unusually great: swerving to an unusual extent, the contacts are struck more obliquely, and the corresponding

*I-I* interval is shorter than it otherwise would be. This tabulated instance is not an isolated one: we have met with many other examples: one of these is incorporated in Table XI (*Dog ME*, Record 28, heavy figures). A similar relation is to be seen in these tables treated as a whole: if the percentage rise in the *S-I* interval at the beginning and during the continuation of the 1:1 response is considerable, the rise in the corresponding *I-I* intervals is inconspicuous: on the other hand, if the percentage rise in the *S-I* intervals is less conspicuous, the rise in the *I-I* intervals is as a rule emphasised. On occasion the swerve may be so great that at the appearance of 1:1 response the *I-I* intervals are actually lower (Table XI *ME*, Record 27) than those obtaining during the period of 2:1 response.\*

Swerve before the wave reaches the contacts is less in the unatropinised than in the atropinised auricle: the greatest percentage rises in the *S-I* intervals (rises of 100 per cent. and more) are seen in the latter only. The reason for this is not far to seek, for the rhythmic shocks which enter the auricle stimulate the vagus nerve endings, and reduce the refractory period of the muscle surrounding the point stimulated: consequently, the first part of the course, along which the excitation waves are propagated, is straighter and the rate of transmission from point to point is not so materially increased.

The first transmission interval of the 1:1 period is generally of exceptional length. In this respect there is a contrast with curves of *A-V* heart-block. In the latter, it is the rule that the intervals increase as the 1:1 responses succeed each other; here they decrease.†

This first long interval is responsible for delay in the appearance of the corresponding intrinsic deflection. The first cycle of the 1:1 responses is always of exceptional length and the intrinsic deflection which terminates it frequently shows change of form (similar to that shown in Fig. 13).

In some instances there is a gradual rise in the length of the intervals preliminary to the return of 2:1 response: the last transmission interval of the 1:1 phase is not infrequently of exaggerated length (Table XI, *MF*, 41 and Table X, *MG*, 17); neither phenomenon is constant.

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\* In isolated instances we have seen them reduced to zero and on a solitary occasion becoming of minus sign, indicating that the distal contacts were first encountered. Swerve of the wave often renders accurate valuation of transmission intervals between pairs of recording contacts impossible. It becomes a factor of real moment, however, only when the rates of stimulation yielding 1:1 response is at its maximal point or near it. In the tables of a previous article<sup>7</sup> the rates of stimulation were for the most part much lower, and the rise in transmission intervals with increasing rate was consequently detected. In Table IX of the present article lower rates of stimulation were also employed; though in one instance (*Dog MK*), the *I-I* interval failed to show change.

† In a previous article<sup>7</sup> two instances of gradual increase in the intervals, up to the point of the first 2:1 response, were recorded. We have not since met with curves of this kind. In those observations the muscle of the superior cava was under investigation, which perhaps accounts for the difference.



*Discussion.* The spontaneous and repeated change from 2:1 to 1:1 response and back again, while the muscle is responding to high rates of stimulation is due, in our view, to lack of uniformity in the length of the effective refractory period of the muscle stimulated. While 1:1 response is in progress the state of partial refractoriness at the instants at which the shocks enter the muscle varies in density from cycle to cycle: when the refractory fibres are concentrated during this period of the cycle (an exaggeration of the condition shown in Fig. 5, cycle 5), the effective refractory period is prolonged beyond the instant at which the next rhythmic shock falls, and as a consequence, there is no response of the auricle: the rest so obtained increases the duration of the effective refractory period at the next response, and simple 2:1 response tends to become established: but it is established on the insecure basis of an overlap of partially refractory tissue. Sooner or later the responsive fibres of this partially refractory period concentrate, and the rhythmic shock, succeeding a response, finds a sufficient number of fibres in the responsive state, and the auricle as a whole follows suit: owing to the short period of rest the effective refractory period of this cycle is lowered and 1:1 response tends to establish itself until the process of concentration, this time of refractory fibres, is repeated. The reason why the first transmission interval of 1:1 response is unusually long is that the partially refractory period of the preceding cycle is longer and more obstructive than that of the cycles which come afterwards. The effective refractory period of the cycle in question is shorter than those of the 2:1 phase: it is the first cycle which just allows response at its termination: the refractory periods of succeeding cycles are shortened in virtue of the doubled auricular rate: the density of the partially refractory period is consequently less when the shocks enter the muscle, and the propagation of the excitation waves is less obstructed.

The lengthened transmission intervals at the end of the 1:1 phase are inconstant. A concentration of refractory fibres in the partially refractory period will delay or obstruct the propagation of the next impulse: if it delays propagation almost to the point of actual obstruction, the transmission interval will show a conspicuous rise in value: if it actually obstructs, 2:1 response will appear at once. Sometimes the beginning of the phase of 2:1 response will be foreshadowed, sometimes it will come abruptly.

The detailed study of transient 2:1 response brings further evidence in favour of our conclusion, that the irregularities seen when the auricle is responding to very high rates of stimulation are all engendered by the duration of the refractory period and by the relation of its end phase of partial refractoriness to the end of the stimulus cycle. We attribute all those apparent changes in conduction, described in the third article of this series,<sup>7</sup> and the complex irregularities in the form, incidence and amplitude of the auricular deflections, directly or indirectly, to this relation.

*Action of vagus upon 2:1 response.*

If the vagus is stimulated during a period of transient or persistent 2:1 response\*, 1:1 response invariably appears after a very brief delay, and if the vagus stimulation is maintained, persists. The delay is no greater than a half second. Fig. 13 is an example of the reaction, which is clearly due to reduction of the refractory period.† Table XIII gives the transmission intervals over the period of change, and the figures of this table may be compared with those illustrating the spontaneous passage from 2:1 to 1:1 response (Tables X and XI). The difference consists in the almost immediate return of the intervals to their values in the 2:1 phase. The first interval (*S-I* and *I-I*) of the 1:1 phase is usually, though not always, prolonged: the second interval may show a minor prolongation. Exceptionally the fall is spread over more cycles.

TABLE XIII.

*Effect of stimulation of vagus nerve upon the auricle giving 2:1 response to high rates of rhythmic stimulation.*

Transmission Times between: (1) Stimulus and intrinsic (1) (proximal contacts),  
(2) Intrinsic (1) (proximal contacts) and intrinsic (2) (distal contacts).

Dog	..	..	MB (Rec. 9).	MB (Rec. 10).	MB (Rec. 8).	MI (Rec. 42).	MF (Record 33).	MF (Record 32).		
Rate of Stimulation	f		510 per min.	480 per min.	487 per min.	458 per min.	530 per min.	530 per min.		
Response			Stimulus to Intrin. 1.	Stimulus to Intrin. 1.	Stimulus to Intrin. 1.	Intrin. 1 to Intrin. 2.	Stimulus to Intrin. 1.	Intrin. 1 to Intrin. 2.		
2:1 response				0-0211 0-0218 0-0218 0-0233 0-0226	0-0205 0-0186 0-0167 0-0162	0-0113 0-0106 0-0102 0-0089	0-0380 0-0416 0-0103	0-0102 0-0365 0-0394 0-0133		
		Vagus on	0-0178	Vagus on	0-0092	0-0374	0-0093	Vagus on	0-0121	
		0-0235	0-0218	Vagus on	0-0096	0-0373	0-0093	0-0374	0-0105-	
		0-0241	0-0288?	0-0204				0-0358		
1:1 response			0-0317 0-0276 0-0232 0-0279 0-0236 0-0242 0-0222 0-0242 0-0271 0-0239 0-0231 0-0264	0-0425 0-0271 0-0232 0-0261 0-0226 0-0238 0-0249 0-0237 0-0239 0-0246 0-0262 0-0249	0-0329 0-0226 0-0188 0-0165 0-0162 0-0181 0-0212 0-0185 0-0193 0-0188 0-0211 0-0250	0-0113 0-0103 0-0107 0-0106 0-0103 0-0106 0-0107 0-0098 0-0089 0-0086 0-0100 0-0083	0-0448 0-0384 0-0391 0-0377 0-0377 0-0399 0-0380 0-0392 0-0356 0-0402 0-0391 0-0397	0-0091 0-0084 0-0096 0-0118 0-0099 0-0102 0-0087 0-0096 0-0093 0-0096 0-0090 0-0087	0-0524 0-0464 0-0430 0-0384 0-0442 0-0377 0-0416 0-0372 0-0366 0-0380 0-0431 0-0386	0-0137 0-0124 0-0154 0-0120 0-0131 0-0115 0-0107 0-0103 0-0109 0-0122 0-0119 0-0111

The distortion of the intrinsic deflection terminating the first 1:1 cycle is well shown in Fig. 13: it is the rule: the first 1:1 cycle is the longest.

\* The rhythmic shocks should stand well above threshold value in this experiment, otherwise, owing to reduced excitability, the muscle will not respond to each shock during the period of vagal stimulation.

† See note on page 129.

Irregularity of the first deflections of the 1 : 1 phase is the rule ; they become regular as the curve proceeds.\*

The reaction of the condition of 2 : 1 response is the expected reaction : the refractory period is reduced and each rhythmic shock now becomes effective. At the first response of the 1 : 1 stage the period of partial refractoriness is still sufficiently prolonged to produce a considerable hindrance to propagation and the corresponding transmission interval is usually unduly prolonged.

*Further observations upon the refractory period.*

*Method.* In testing the refractory period of the auricular muscle we have employed a second method. The same apparatus is used (see Fig. 1), with the exception that the two secondary coils are connected to separate pairs of stimulating electrodes. The left hand inductorium stimulates the heart rhythmically at one point,† the right-hand coil tests the refractory period at a different point of the auricular surface. The object of using different points of stimulation is to avoid rhythmically exciting the nerve endings in the muscle whose refractory period is tested. It involves a double measurement : the boundary of response and no response must be estimated at both the beginning and end of the refractory period.‡

Now this method, useful though it is for certain purposes, introduces an error. The error arises out of the relative positions of the two pairs of stimulating electrodes and of the contacts recording response, the manner in which it arises may be explained by means of a diagram (Fig. 6). To the right of this diagram is a triangle, *A, B, C*, the angles of which represent : *A*, the point stimulated rhythmically ; § *B*, the point at which the refractory period is measured by means of test shocks : and, *C*, the point at which responses of the muscle are recorded. It is supposed, for purposes of argument, that an excitation wave takes 0.03 of a second and 0.04 of a second to travel from *A* to *B* and *C* respectively, and that it takes 0.03 of a second to travel from *B* to *C*. In the main part of the diagram, and reading from left to right, the times at which the rhythmic shocks enter and give response at *A* are charted as black circles. The waves of excitation starting at *A* travel to *B*, and the actual refractory periods in the muscle at *B* are charted as black rectangles. The period begins at *b* (0.03 of a second after *A* is excited) and ends at *e* (say 0.14 of a second later). The waves also travel to *C*,

\* For reasons which are not clear to us, the vagus has usually reduced the irregularity of the intrinsic deflections to uniformity, and has lowered the transmission intervals, more speedily in these experiments than in the circumstances previously described. We regard this difference as being probably accidental.

† This coil and its electrodes are dispensed with if the heart is responding to inherent impulses.

‡ In a heart driven rhythmically the measurements are confined to the upper string shadow as before described ; but in a heart responding to inherent impulses, the measurements are referred to the intrinsic deflection of the inherent beat, which is recorded by the lower string shadow.

§ Or in the case of a spontaneous rhythm, the point from which the spontaneous rhythm arises.

the muscle under the recording contacts, and here the refractory period is represented as a white rectangle in which the record of the electrical response is shown. Now the shocks which test the refractory period enter the muscle at  $B$ ; if a shock enters immediately after the ending of the refractory period (as at  $x$ ) it yields a response and the wave of excitation is propagated to the recording contacts at  $C$ ; for the whole stretch of muscle between  $B$  and  $C$  is responsive when the excitation wave passes through it. The wave propagated by the testing shock takes 0.03 of a second or more\* to reach  $C$ . If, however, a shock falls at the end of the responsive period (*i.e.*, shortly before  $b$ ) it excites the muscle and the wave of excitation is propagated towards  $C$ , but it will not reach  $C$ , since this muscle area receives the rhythmic impulse in the interval (0.03 of a second) during which the wave is travelling from  $B$  to  $C$ . The last test shock which can excite the muscle at  $B$  and yet yield a response at  $C$  will fall at the point  $Y$ , which lies 0.03 of a second in front of  $z$ , the beginning of the rhythmic refractory period of muscle  $C$ . Thus while the refractory period has an actual duration  $bc$ , it will be measured as having a duration  $ye$ . The interval  $yb$  is calculable, if we know the transmission times between the angles of the triangle. It is equal to  $BC - (AC - AB)$ ; in the instance given it is  $0.03 - (0.04 - 0.03)$  of a second  $= 0.02$  of a second; and the refractory period of 0.14 of a second will be measured at 0.16 of a second. Now the formula given applies to all positions in which the electrodes and contacts are likely to be placed, and it will be apparent on consideration that the greater the transmission interval  $AC$  or the smaller the intervals  $AB$  and  $BC$ , the less will be the error. But the error will not be reduced to zero, unless the transmission interval  $AC$  is equal to the combined transmission intervals  $AB$  and  $BC$ . In other words, there will be an error unless the rhythmic excitation waves reach  $C$  by passing over  $B$  en route. If the precise line taken by the rhythmic excitation waves were known, the error could be eliminated by placing the testing electrodes on its path; but it is never precisely known, for the reason that the excitation wave follows bands of muscle in the auricle and does not necessarily course along a straight line.† The possibility of material error is always present. It becomes necessary, therefore, to test the error deliberately and to make allowance for it where this is possible, a procedure which will be described in its proper place.‡

\* We say "more," because at the beginning of the responsive period the transmission interval may be prolonged.

† And in the case of spontaneous rhythm the point from which the rhythmic waves spring may not be precisely known.

‡ It should be noted that the largest error is introduced when the recording contacts are placed between the point of rhythmic stimulation and test stimulation. The error is then a gross one. It may be asked why the error cannot be eliminated by bringing the chosen points nearer together. If  $B$  and  $C$  lie close together, the electrical record of response is confused by the record of the current of stimulation. If  $A$  and  $B$  are brought closer together, the effects of the rhythmic stimulation of the nerves in the muscle in the region  $A$  will spread over to region  $B$  and the whole object of separating  $A$  and  $B$ , namely, to avoid this particular disturbance, is defeated. If, on the other hand,  $A$  is a point in which rhythmic impulses are arising spontaneously, the close approach of  $B$  might be calculated to disturb the rate of these impulses.

*Observations.* The second method of estimating the refractory period of the auricle has been employed in an attempt to arrive at normal values in the unatropinised heart. We give the readings in Table XIV for four dogs. In the first column of each section are the readings for the refractory period as ascertained by the first method of observation, namely, by rhythmically stimulating a point on the body of the auricle and by throwing in the testing shocks at the same point of the atropinised auricle. The values found for the refractory period are 0.079, 0.041, etc., of a second (see line *D* of Table XVI). In the second column of each section (Table XIV) are the readings obtained when the rhythmic shocks are applied to the muscle of the superior cava outside the reflection of the pericardium, the test shocks

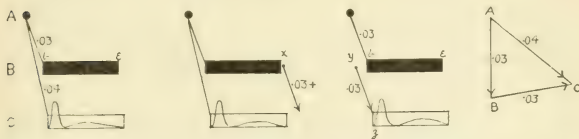


Fig. 6. A diagram illustrating a source of error in attempting to measure the refractory period, when the muscle fibres tested are not those in which the rhythm is originating.

being applied to the original point on the body of the auricle. The two limits of the refractory period, as ascertained by this method, are indicated by the horizontal lines (*RP*) of the tables. The periods over which these auricles were unresponsive are seen to be 0.107, 0.153, 0.095 and 0.153 of a second; and these values are given in line *C* of Table XVI. Now these four values for the refractory period exceed those obtained by the first method in each instance, and the difference is in large part due to local stimulation of the vagal fibres under the condition of the first method. But that is not the only reason of the difference, for a material error creeps into the second method, as has been explained. The second method over-estimates the refractory period by a variable quantity. To obtain an idea of this error we repeat the two series of observations upon the same auricles atropinised (Table XV). These observations are summarised in Table XVI (lines *A* and *B*). To take as an example *Dog LX*, the value given for the refractory period by the second method under atropine (Table XV), is 0.176 of a second; the true value, as ascertained by the first method, is 0.124. The over-estimation by the second method is 0.052 of a second. This substantial error we ascribe to the factor of transmission (Fig. 6), which influences the values given by the second method. The value of the refractory period, ascertained by the second method when this auricle was unatropinised, was 0.153 of a second; from



TABLE NV.

	<i>Day L.V.</i> Rate 210. (Cycle of 0.286 sec.)	<i>Day I.V.</i> Rate 186. (Cycle of 0.322 sec.)	<i>Day I.V.</i> Rate 236. (Cycle of 0.261 sec.)	<i>Day I.Z.</i> Rate 180. (Cycle of 0.333 sec.)
	Atropinised.	Atropinised.	Atropinised.	Atropinised.
R. and M.E. on S.V.C.	R. on S.V.C.	R. on S.V.C.	R. and M.B. R. on S.V.C.	R. on M.E. R. on I.V.C.
on body of auricle at one point, (1st method) (2nd method)	M.E. on body of auricle at one point, (1st method) (2nd method)	M.B. on body of auricle, one point, (1st method) (2nd method)	M.B. on body of auricle, one point, (1st method) (2nd method)	M.B. on body of auricle at one point, (1st method) (2nd method)
0.232 <i>m</i>	0.232 <i>m</i>			
0.297 <i>m</i>	0.297 <i>m</i>			
0.200 <i>m</i>	0.181 <i>b</i>			
0.191 <i>m</i>	0.171 <i>m</i>			
0.184 <i>m</i>	0.160 <i>b</i>			
0.182 <i>m</i>	0.137 <i>b</i>	0.196 <i>b</i>	0.129 <i>b</i>	0.199 <i>b</i>
0.179 <i>m</i>	0.129 <i>b</i>	0.196 <i>b</i>	0.120 <i>m</i>	0.178 <i>b</i>
0.165 <i>b</i>	0.177 <i>m</i>	0.191 <i>b</i>	0.112 <i>b</i>	0.172 <i>b</i>
0.173 <i>b</i>	0.129 <i>b</i>	0.188 <i>m</i>	0.106 <i>m</i>	0.255 <i>b</i>
	0.127 <i>m</i>	0.184 <i>m</i>	0.104 <i>m</i>	0.250 <i>m</i>
				0.148 <i>m</i>
				0.230 <i>b</i>
				0.141 <i>m</i>
R. P. . . . .				
	0.131 <i>b</i>	0.121 <i>m</i>	0.101 <i>b</i>	0.137 <i>b</i>
	0.125 <i>m</i>	0.121 <i>m</i>	0.095 <i>b</i>	0.128 <i>m</i>
	0.123 <i>b</i>	0.111 <i>m</i>	0.079 <i>m</i>	0.198 <i>m</i>
	0.121 <i>m</i>	0.104 <i>m</i>	0.079 <i>m</i>	0.186 <i>b</i>
	0.119 <i>m</i>	0.104 <i>b</i>	0.079 <i>m</i>	0.181 <i>m</i>
	0.101 <i>m</i>	0.103 <i>m</i>	0.072 <i>m</i>	0.168 <i>m</i>
	0.095 <i>b</i>	0.046 <i>b</i>	0.070 <i>b</i>	0.114 <i>m</i>
		0.035 <i>m</i>		0.085 <i>b</i>
		0.035 <i>b</i>		0.041 <i>b</i>
				0.036 <i>m</i>
				0.028 <i>b</i>
				0.027 <i>m</i>
R. P. . . . .				
	0.027 <i>b</i>			0.027 <i>b</i>
	0.024 <i>b</i>	0.002 <i>b</i>	0.019 <i>b</i>	0.025 <i>m</i>
	0.011 <i>b</i>		0.017 <i>m</i>	0.022 <i>m</i>
			0.014 <i>m</i>	0.021 <i>m</i>
			0.013 <i>m</i>	0.015 <i>b</i>
Estimated R. P. . . . .	0.133	0.124	0.102	0.139
	0.142	0.176	0.117	0.193

R. = rhythmic, and M. P. = marked and break, shocks.



this we subtract the error 0.052 of a second), as this is tabulated in the atropinised heart, and obtain a corrected value of 0.101 of a second. The corrected values\* for the other animals are obtained in similar fashion. The four corrected values obtained are those of the refractory periods of heart beating at from 180 to 230 per minute: in the four experiments they are sufficiently uniform: they average 0.097 of a second. In the atropinised auricle (line *B*) the average value is 0.127 of a second. It would appear from these observations that the refractory period in the atropinised heart, beating at a rate of about 200 per minute, is 0.03 of a second longer than in the unatropinised heart, in the conditions of our experiments, a difference which it is natural to ascribe to loss of vagal tone under atropine. We assume that the error is the same for atropinised and unatropinised auricles: this can be the case only if the rate of conduction in the auricle is uninfluenced by atropine. Such we find to be the case (Table XVII) at rates of stimulation within those used in the foregoing experiments. Atropine has little or no influence upon the transmission intervals at heart rates of 250 and under: consequently we may conclude that atropine does not materially affect the rate of fibre conduction. That atropine would often increase the transmission intervals at higher rates of stimulation we do not doubt: this tendency is actually shown by one observation of Table XVII (namely, *Dog M.G.*), in which the rate of stimulation was 257 per minute. Such effects are to be explained on the ground that atropine has a lengthening influence upon the refractory period, and thus tends, at high rates of stimulation, to close the gap between the end of the refractory period and the next rhythmic shock.

That the refractory period is a little longer under atropine than in the unatropinised heart is indicated not only by the observations now cited, but by others. Thus, irregularities in the amplitude of the intrinsic deflections and transient 2:1 block (see Table XVIII) appear at somewhat lower rates in the atropinised than in the unatropinised animal: so also does persistent 2:1 block. The difference is not a very great one, but is sufficiently constant to be noted. It is a difference of some 50 beats per minute, and represents a time difference of about 0.017 of a second.† Thus, if we take the evidence from all sources, it seems clear that the refractory period is raised by atropine, when this drug is given in the conditions of our experiments: the precise extent of this rise is not known, though there is sufficient evidence that it is not very considerable.

Upon measurements of the refractory period, described in this section, we do not wish to lay undue stress: we publish them largely to point out some of the difficulties experienced in attempting precisely to measure the refractory period in the unatropinised heart.

\* In the case of *Dog L.W.* a correction would appear to be unnecessary.

† Difference in the length of cycle in an auricle beating at 400 and 450, respectively.



TABLE XVI.  
*Refractory period.*

R. P. estimated	Dog L.W. Rate 207.	Dog L.X. Rate 186.	Dog L.Y. Rate 230.	Dog L.Z. Rate 180.
A. away from point of rhythmic stimulation under atropine	0.133	0.176	0.117	0.193
B. at point of rhythmic stimulation under atropine	0.142	0.124	0.102	0.139
Overestimate in A		<b>0.052</b>	<b>0.015</b>	<b>0.054</b>
C. away from point of rhythmic stimulation, unatropinised	0.107	0.153	0.095	0.153
Corrected values for unatropinised auricle	<b>0.107</b>	<b>0.101</b>	<b>0.080</b>	<b>0.099</b>
D. at point of rhythmic stimulation, unatropinised	<b>0.079</b>	<b>0.041</b>	<b>0.093</b>	<b>0.075</b>

TABLE XVII.  
*Transmission intervals before and after atropine.*

Dog.	Auricular rate.		Stimulus to intrinsic interval in secs.		Intrinsic to intrinsic interval in secs.	
	Before.	After.	Before.	After.	Before.	After.
<i>MI.</i>	180	183	0.0095	0.0093	0.0343	0.0370
<i>MH.</i>	206	208	0.0036	0.0036	0.0338	0.0358
<i>MD.</i>	240	245	0.0060	0.0060		
<i>MF.</i>	254	253	0.0099	0.0100		
<i>MG.</i>	257	257	0.0074	<b>0.0091</b>	0.0604	<b>0.0645</b>
<i>MK.</i>	284	286	0.0097	0.0097	0.0382	0.0407

TABLE XVIII.  
*Rate of stimulation required to produce transient 2 : 1, and 1 : 1 response.*

Dog.	Normal.	Atropinised.
<i>MB.</i>	452	400
<i>MC.</i>	552	445
<i>MD.</i>	450	384
<i>ME.</i>	475	432
<i>MJ.</i>	440	375

*Relation of foregoing observations to auricular flutter.*

The relation between flutter and refractory period on the one hand, and the rate at which the excitation wave is propagated on the other, has been discussed briefly in a previous article<sup>4</sup>; but the data at our disposal at the time were insufficient to permit of much beyond a general survey. We arrive at several conclusions from the present observations, which appear to us to have a fundamental bearing upon the subject under discussion.

In the first place it is clear that in considering the influence of enhanced rate upon the auricle, we may leave the rate of fibre conduction out of account. As we have been able to show, the rate of fibre conduction is undisturbed at rates such as prevail in flutter.\* We may not similarly dismiss the rate of transmission from point to point; this is almost always adversely affected when the auricular rate rises to the levels prevailing in flutter (*i.e.*, 350 and more per minute). The distinction is an important one, and chiefly because, as we have demonstrated, the widening of the transmission intervals is due to the length of the refractory period. We may draw the general conclusion from our present observations that *whenever, as a result of increased rate of beating, the speed at which the excitation wave is conveyed from point to point of the auricle is reduced below normal, the crest of the excitation wave is flowing through muscle which is in a partially refractory state, and that the lessened rate of propagation is due to this cause.* This conclusion applies not only to the auricle, responding to rhythmic shocks, but to that which is driven by a circulating wave of excitation, *i.e.*, to the fluttering auricle. Now a decreased rate of propagation is the rule in what we have termed pure flutter,<sup>6</sup> though there appear to be occasional exceptions. We may conclude, therefore, that even in pure flutter it is the rule that the crest of the circulating wave is flowing always through muscle in a partially refractory state. That is tantamount to the assertion that the gap between the crest of the wave and its wake of absolute refractoriness is a small one, and that this gap is bridged by fibres, more or less numerous, which are refractory as the wave passes.

It is also possible to conclude from our observations that *whenever, as a result of increased rates of beating, the electrogram becomes irregular, the intrinsic deflections displaying variations in amplitude, form or incidence, the crest of the excitation wave is similarly affected, being deflected from side to side upon a sinuous course, by barriers of refractory muscle.* This conclusion is at once and universally applicable to impure flutter.† In a previous article<sup>4</sup> it has been concluded mainly from direct observation that in impure flutter this sinuosity of the wave exists; we arrive again at the same conclusion from other data, and widen it by recognising the precise nature of the barriers.

\* Actually the rate of fibre conduction is undisturbed at much higher rates than these. Separate observations, to be recorded in a later article, show that the fibres are capable of conducting normally when the auricle is beating as rapidly as 800 to 1,100 per minute. The rate of beating is probably without influence upon fibre conduction in any circumstance.

† It is applicable, as we shall see, to fibrillation also.

To sum up, when the dog's auricle is thrown into a state of flutter, pure or impure, a wave of excitation circulates continuously in the auricle: the rate at which this wave travels is not as a rule normal: it is lower than normal because its progress is through tissue in which responsiveness is but partially recovered. To be maintained, a gap between the crest of the wave and the wake of effective refractoriness must remain: this gap is a small one in flutter, and it is imperfect in that it is constituted by tissue of which the fibres are not all in the responsive state.

We may at this stage enquire if direct evidence of the extent of this gap can be brought forward.

*The responsive gap in flutter.*

On three occasions we have had an opportunity of testing the length of refractory and responsive periods during long continued flutter. The enquiry is beset with minor difficulties, which have been foreshadowed in the preceding pages. In one instance we have obtained conclusive evidence of a short gap and have been able to obtain a measure of it: in two instances we have been unable to demonstrate the gap or its extent. The method employed has differed a little in the different observations, which will be described separately.

*1st experiment. (Dog L.V.)* A slightly impure flutter was started in this auricle by rhythmic stimulation. The excitation waves were found to be travelling up the terna terminalis and from the base to the tip of the right appendix. The rate of movement averaged 508 per minute (length of cycle 0.1180 of a second). This period of flutter lasted over an hour and records were taken by means of a direct lead placed on the tip of and in line with the appendix, while rhythmic break shocks were sent into the appendix at its base and 2 centimetres from the contacts. This distance is of importance in that if such shocks enter the muscle in the immediate neighbourhood of the recording contacts, any recorded responses to these shocks might be attributed to the lowering influence which such shocks are known to exert locally upon the refractory period. The second fibre was used to record the rhythmic shocks and the measurements of the plates are expressed in two columns in Table XIX. The first column gives the interval between the intrinsic deflection and the succeeding testing shock: it indicates the phase of the flutter cycle at which the testing shock entered the muscle. The second column gives the length of the corresponding cycle, as measured from the preceding to the succeeding intrinsic deflection. The flutter being slightly impure, the lengths of these cycles vary throughout in slight degree, but there are six (those in heavy type) which are unusually short. If these six short cycles were diffused throughout the column, a less confident conclusion could be drawn from them: but that is not the case: they are grouped together. These cycles, terminated as they are by slightly premature deflections, are cycles standing with definite time relations to

the testing shocks. These shocks are signalled between 0.0576 and 0.0778 of a second, after the first intrinsic deflections of the corresponding cycles are recorded. The whole period of response extends for approximately 0.02 of a second, over a cycle of 0.118 of a second in duration. That is the extent of the gap. The period of invariable response is less than this: it is approximately 0.01 of a second in duration, extending between the values 0.0620 and 0.0738 of a second. This experiment affords clear evidence of a very short and partially responsive gap.\*

*2nd experiment.* (*Dog MB.*) A slightly impure flutter was started by rhythmic stimulation in a fully atropinised auricle.† It had lasted 30 minutes when it was tested by means of make and break shocks well above threshold value.‡ It proceeded for 15 minutes longer. The excitation wave flowed in the same direction as in the preceding experiment: the recording contacts and stimulating electrodes were similarly placed: but the distance between the two was less than 1 centimetre.§ The rate of the flutter was 355 per minute and the length of its cycle averaged 0.1688 of a second. The result is given in Table XIX. There is but a slight variation in the length of the cycles and no evidence that these are altered in length by the testing shocks.

This flutter ended spontaneously at 45 minutes after its onset, and the original rhythmic break shocks were re-applied in an attempt to re-establish it. The attempt failed because the auricle failed to respond to every shock: a condition of transient 2:1 response was seen and soon afterwards 2:1 response became established. Now the rate at which these shocks entered the auricle was the same as had previously been used successfully to induce the flutter. On the previous occasion the auricle responded repeatedly and completely to the shocks: its subsequent failure to respond to the original rate of stimulation immediately after the flutter had ended signifies that the refractory period in the auricle had risen a little meanwhile, at once suggesting that the spontaneous ending was brought about as a result of this change. The observation was the more fortunate because the rate at which the rhythmic shocks were applied was almost precisely that of the

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\* As the column stands, the gap *appears* to be in the centre of the cycle. This is due to the time taken for the wave to flow from the point stimulated to the recording contacts, 2 centimetres away. To render the relation more apparent the readings of the intrinsic to stimulus intervals should be moved on by the amount of this transmission interval. As the precise transmission rate is unknown, we prefer to leave the values unaltered; but supposing the rate of transmission to be 500 millimetres per second, a fair supposition, the time taken to travel 20 millimetres would be 0.04 of a second. This addition would bring the stimuli giving response to the end period of the cycle.

† Such an event is extremely unusual, atropinised auricles rarely show after-effects, and this is the only occasion upon which we have witnessed a long-continued after-effect.

‡ The effectiveness of the shocks was tested and proved as soon as the flutter ended.

§ The distance was reduced because the auricle was atropinised—the vagus endings being paralysed, the rhythmic shocks could not influence the refractory period at the recording contacts.

preceding flutter (the rates were 355 and 359 per minute, respectively).<sup>\*</sup> A rise of the refractory period would close the gap between the crest and wake of the circulating wave and bring it to an end. To suppose that by a slight rise the gap was closed, is consistent with our failure to discover a responsive period in the muscle while it fluttered: the gap may be supposed to have been almost negligible.

*3rd experiment. (Dog M.D.)* Flutter having a rate of 459 per minute was produced in this auricle by rhythmic stimulation of the right appendix. The excitation waves were travelling up the tania and appendix: the flutter had lasted 20 minutes, when it was tested by means of rhythmic shocks.<sup>†</sup> These shocks were sent into the base of the appendix, and records of the auricular movements were taken by means of contacts placed on the tip of the appendix, 25 millimetres away: the contacts were subsequently moved quite close to the stimulating electrode without changing the result. The flutter stopped spontaneously 43 minutes after its onset. As in the last experiment, the shocks failed perceptibly to influence the length of the flutter cycles, although they fell in all phases of these cycles (Table XIX).

In considering the last two experiments, in neither of which could the extent of the gap be determined, it is to be remembered that the method of testing the auricle which was used is comparable to the method described at page 121. It is subject to error, because there is no guarantee that the excitation waves are travelling precisely in the line of stimulating electrodes and recording contacts: this method, which is the only one available, usually over estimates the duration of the refractory period, under-estimates the duration of the responsive gap. In both experiments the stimulating electrodes and recording contacts were arranged in a fashion calculated to reduce the error as far as possible, but, as experience has shown, it is not always possible wholly to eliminate it. We judge from our inability to demonstrate the existence of the gap, that the gap was of very small duration: it could scarcely have exceeded two or three hundredths of a second in length.

<sup>\*</sup> The inability of the auricle to respond immediately after the ending of the flutter to stimulation at the rate of the flutter cannot be allowed to weigh, in concluding that the ending was due to rise of the refractory period. The auricle as a whole is more likely to respond to circulating excitation waves than to shocks, at these critical rates, for the former enter the muscle on a broader front. The auricle breaks into 2:1 response, as the rate of stimulation is raised, at a somewhat higher rate if the shocks are strong. Although the overlapping readings of Tables II and III are independent of the strength of stimulus, yet there is no doubt that if the strength of shocks is not much above threshold, the factor of strength of shock creeps in; but the explanation is probably somewhat different from that underlying the phenomenon observed by Lucas and others. If fibres under and surrounding the point stimulated are in a dense state of partial refractoriness, the chance of response in the auricle as a whole will be greater, the more the stimulus spreads as an effective stimulus into the muscle. An excitation wave started in a few fibres responding at the centre, may be obstructed from spreading, while if many surrounding fibres also respond to a stronger stimulus the chance of the wave obtaining an outlet will be increased. We explain the influence of the strength of stimulation upon the level of rate up to which 1:1 response is maintained on these lines. In the atropinised auricle, an excitation wave which once finds its way from the stimulating electrodes to the recording contacts always spreads over the whole auricle: 1:1 response in one large area and 2:1 responses in another large area we have never seen. We believe it does not occur because a wave travelling in the auricle maintains a broad front and the channels open to its spread are more numerous than are those presented to an excitation wave radiating from a point of stimulation.

<sup>†</sup> Subsequently tested and found to be well above threshold value.

TABLE XIX.

*Refractory period in auricular flutter.*

<i>Dog L V.</i> Rate per min. 508. Average length of cycle 0-1180 in secs.		<i>Dog M B.</i> Rate per min. 355. Average length of cycle 0-1688 in secs.		<i>Dog M D.</i> Rate per min. 459. Average length of cycle 0-1308 in secs.	
Time from preceding intrinsic to stimulus.	Length of corresponding cycle.	Time from preceding intrinsic to stimulus.	Length of corresponding cycle.	Time from preceding intrinsic to stimulus.	Length of corresponding cycle.
Seconds.	Seconds.	Seconds.	Seconds.	Seconds.	Seconds.
0-0009	0-1219	0-0027	0-1702	0-0013	0-1348
0-0026	0-1194	0-0085	0-1708	0-0030	0-1302
0-0060	0-1222	0-0161	0-1705	0-0047	0-1290
0-0094	0-1194	0-0171	0-1702	0-0094	0-1321
0-0117	0-1146	0-0215	0-1681	0-0138	0-1308
0-0185	0-1211	0-0300	0-1706	0-0144	0-1330
0-0202	0-1230	0-0351	0-1697	0-0165	0-1292
0-0253	0-1143	0-0393	0-1694	0-0186	0-1308
0-0276	0-1222	0-0411	0-1673	0-0229	0-1325
0-0320	0-1133	0-0560	0-1714	0-0231	0-1287
0-0356	0-1173	0-0630	0-1709	0-0236	0-1303
0-0366	0-1220	0-0637	0-1698	0-0261	0-1347
0-0513	0-1143	0-0722	0-1687	0-0329	0-1293
<b>R 0 0576</b>	<b>0 1089</b>	0-0844	0-1707	0-0341	0-1281
0-0614	0-1141	0-0882	0-1705	0-0355	0-1332
<b>R 0 0620</b>	<b>0 1071</b>	0-0926	0-1684	0-0369	0-1341
<b>R 0 0667</b>	<b>0 1104</b>	0-0970	0-1709	0-0404	0-1282
<b>R 0 0730</b>	<b>0 1065</b>	0-1002	0-1694	0-0510	0-1347
<b>R 0 0738</b>	<b>0 1054</b>	0-1003	0-1689	0-0574	0-1338
0-0760	0-1157	0-1067	0-1698	0-0655	0-1307
<b>R 0 0778</b>	<b>0 1103</b>	0-1191	0-1707	0-0678	0-1289
0-0830	0-1163	0-1213	0-1658	0-0684	0-1348
0-0831	0-1207	0-1269	0-1719	0-0735	0-1346
0-0862	0-1181	0-1303	0-1684	0-0739	0-1287
0-0874	0-1208	0-1363	0-1683	0-0784	0-1282
0-0910	0-1209	0-1499	0-1695	0-0813	0-1352
0-0913	0-1170	0-1516	0-1696	0-0815	0-1292
0-0945	0-1158	0-1646	0-1657	0-0844	0-1318
0-1000	0-1150	0-1681	0-1687	0-0873	0-1318
0-1042	0-1200			0-0886	0-1300
0-1058	0-1241			0-0908	0-1272
0-1128	0-1164			0-0938	0-1299
				0-0942	0-1338
				0-0988	0-1300
				0-0996	0-1291
				0-1112	0-1331
				0-1167	0-1326
				0-1207	0-1343
				0-1280	0-1283
				0-1340	0-1358

In a previous article<sup>4</sup> it has been stated that flutter may sometimes be brought to an end by applying rhythmic shocks to the auricle (Table XX); it has also been stated that rhythmic stimulation may on other occasions produce no such effect. These observations have been confirmed in the present series of experiments: much more frequently than not the flutter continues uninterruptedly. The reason why flutter is brought to an end on one occasion and not on another has been discussed in a previous article; these observations and the explanation previously given harmonise with our

recent observations upon the length of the gap.\* The gap proving to be a short one, it is to be expected that rhythmic shocks applied would very rarely terminate the flutter, even though the cycles are to a slight extent disturbed, as in the first experiment here related.

TABLE XX.

		Duration of flutter.	Brought to an end by :—
<i>Dog K C.</i>	Impure flutter (rate about 514 per min.).	8.3 mins.	A series of about 20 rhythmic shocks at a rate of 277 per minute in each instance.
		3.0 ..	
		4.0 ..	
<i>Dog L M.</i>	Impure flutter (rate about 409 per min.).	5.0 mins.	10-15 rhythmic shocks (rate 367 per minute).
		5.5 ..	A series of about 20-30 rhythmic shocks (rate 367 per min.), after several unsuccessful applications.
<i>Dog L V.</i>	Slight impure flutter (rate about 491 per min.).	9.0 mins.	A series of make and break shocks (rate 193 per min.), after several unsuccessful applications.
		58 mins.	A series of rhythmic shocks (rate 200 per min.), after several unsuccessful applications.

In pure flutter in the dog the rate lies usually between 350 and 450 per minute, the length of the cycles lying usually between 0.17 and 0.13 of a second; the duration of the gap of responsiveness, or partial responsiveness, is probably less than 0.07 of a second at the lowest rate, and less than 0.03 at the highest rate. These values are obtained by subtracting 0.10 of a second, the approximate value of the effective refractory period.

For human flutter the rates are 200 to 350, and the auricular cycles have a length of from 0.3 to 0.17 of a second; that is so because the length of the muscle paths is longer in the human than in the dog's heart. Assuming that the refractory period of human auricular muscle is not appreciably greater than that of the dog's muscle, for similar heart rates, then it would seem that the length of the gap of responsiveness or partial responsiveness in human flutter may be greater than in flutter as it occurs in experiment upon the dog.†

\* In the previous article, however, the duration of the gap was much over-estimated in the footnote to page 327.

† The use of atropine as a therapeutic remedy in flutter suggests itself, but if the gap is long atropinisation might fail to close it and bring the flutter to an end. Atropine is not a remedy to give lightly in flutter, for it might dangerously enhance the ventricular rate, unless its use were confined to cases of flutter exhibiting a high grade of block. In these it should certainly be tried in full doses.



*Production of flutter.* In a previous article it has been pointed out that when as a result of high rates of stimulation the transmission intervals begin to increase and the curves of direct leads begin to be irregular, a stage has been reached at which "after-effects" of stimulation are anticipated. In that article,<sup>1</sup> the view was held that a stage had been reached at which local blocks were instituted, whereby the excitation waves were from time to time forced to travel in a single direction. This unidirectional course is theoretically necessary to the onset of flutter. The nature of these barriers has now become clear: they are barriers of refractory muscle. *The circus movement which underlies flutter is provoked when an effective shock enters auricular muscle while the latter is in a critical condition. The critical condition is the condition of partial refractoriness, brought about by a high rate of beating.*

*Note.*—In curves from the frog's auricle published by Engelmann (*Archiv. f. Anat. u. Physiol., 1902, Physiol. Abth., Suppl. Bd., 1*), comparable curves to that of Fig. 13 of the present paper are shown. They are ascribed by Engelmann to a "positive-bathmotropic" effect of the vagus, by which he means that excitability was raised under vagal stimulation. In the light of our experiments this explanation is clearly untenable. Engelmann had not to deal with raised excitability but with shortened refractory period. The particular figures referred to (Figs. 9 to 12 of his paper) form the chief evidence in support of his famous theory that "excitability" and "contractility" are wholly independent functions of cardiac muscle: for these curves purport to show the coincident appearance of "positive-bathmotropic" (raised excitability) and "negative-inotropic" (lowered contractility) effects. In point of fact they do not do so. If, as we believe, the remaining evidence of his paper is equally open to objection, the case, which Engelmann states in this paper, falls to the ground; in any case it is very materially weakened by our present observations.

#### SUMMARY OF CHIEF CONCLUSIONS.

1. The absolute refractory period of dog's auricular muscle beating at rates of about 200 per minute is reduced to one-fifth or one-sixth its full value by vagal stimulation.
2. The absolute refractory period of the atropinised auricle is reduced by increase of the auricular rate up to about 290 per minute: after this rate is passed the measure of the refractory period remains the same or increases, owing to the development of a phase of partial refractoriness.
3. Succeeding shocks fall during the partially refractory phase when stimulation rises to this approximate rate, consequently the electrogram



becomes irregular and the rate at which the excitation wave is transmitted from point to point of the muscle falls. Shortly the auricle fails to respond to some of the stimuli.

4. The vagus has no influence on fibre conduction in the dog's auricle.

5. If the speed at which excitation waves are transmitted from point to point in the auricle is lowered as a result of the high rate of response of the muscle, vagal stimulation raises the speed to its normal level. It does so by reducing the refractory period. The defects in conduction witnessed in auricles responding to high rates of stimulation are produced by barriers of refractory muscle.

6. When in flutter and in impure flutter the speed at which the excitation waves are transmitted from point to point is observed to be reduced, or when, in the last condition, the excitation waves are propagated along sinuous courses, the crests of the waves are flowing through muscle in a partially refractory state. The excitation waves are impeded by smaller or larger barriers of refractory muscle.

7. In flutter, produced experimentally in the dog's auricle, the gap between the crest of the circulating wave and its wake of absolute refractoriness is a short one.

8. Atropine is without effect on fibre conduction, but by abolishing vagal tone it raises the length of the refractory period, and would tend in the fluttering auricle to close the gap.

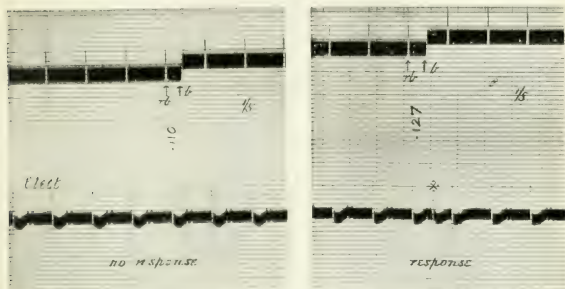
9. The circus movement which underlies auricular flutter is provoked when an effective stimulus enters the muscle while the latter is in a partially refractory state.

10. The observations here recorded explain certain effects witnessed by Engelmann, effects which he appears to have wrongly interpreted, and upon which he chiefly based his conclusion, that "excitability" and "contractility" are wholly independent properties of cardiac muscle.

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- <sup>15</sup> TRENDLENBURG. Archiv. f. d. ges. Physiol., 1911, CXLI, 378.

The standard of the following electrograms is approximately 1 centimetre = 3 millivolts.



Figs. 7 and 8. *Dog M.H.* (Records 57 and 56.) The upper curve of each figure signals the shocks. *a*, rhythmic break shocks; *b*, break testing shock. The lower curves are electrograms taken by a direct lead from the auricle; Fig. 2 shows a response at 0.127 of a second, Fig. 1 shows none at 0.110 of a second. Time lines in fifths of a second.

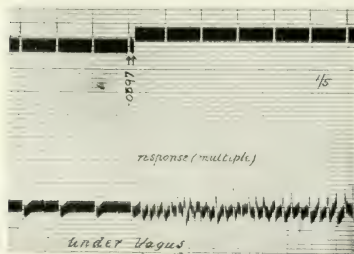


Fig. 9. *Dog M.H.* (Record 52.) A similar curve, showing response after an interval of 0.0397 of a second, while the auricle is under vagal stimulation. The response is not single, but multiple. This multiple response under vagal stimulation is frequent; it will be spoken of in a later article.



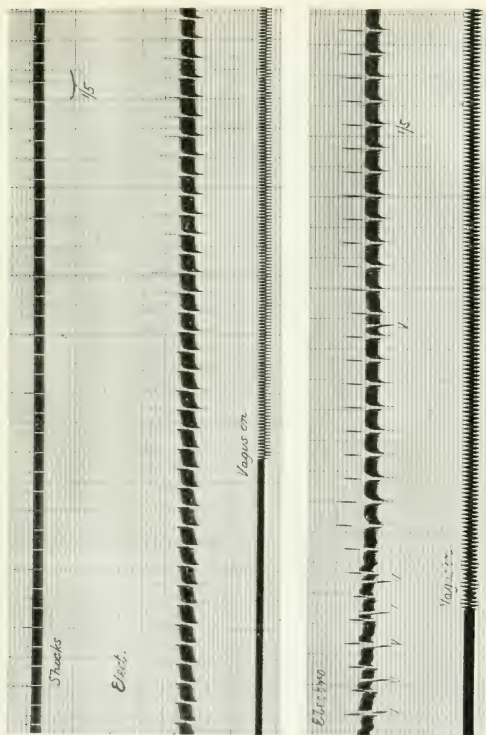
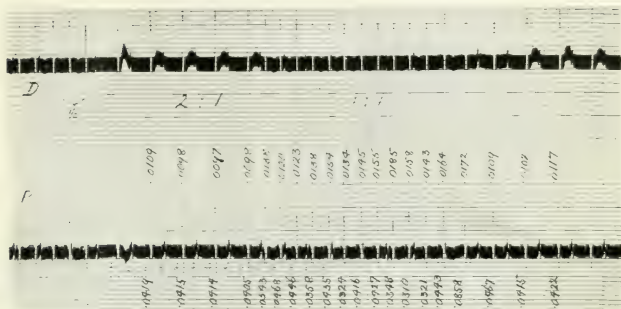


Fig. 10. Dog M.C. (Record 50). The auricle is responding to rhythmic break shocks thrown in at a rate of 450 per minute. The shocks are signalled above, and the responses of the auricle below. The electrogram shows irregularity in the heights of the intrinsic deflections; this irregularity is abolished by vagal stimulation. Time lines in fifths of a second.

Fig. 11. Dog M.K. (Record 11). A similar electrogram of an auricle responding to rhythmic break shocks at a rate of 386 per minute; under vagal stimulation the amplitude of the intrinsic deflections becomes constant. V=ventricular effect. Time lines in fifths of a second.









## OBSERVATIONS UPON FLUTTER AND FIBRILLATION.

### PART VII.—THE EFFECTS OF VAGAL STIMULATION.\*

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ANY theory intended to explain flutter and fibrillation, must, if sound, be capable of explaining the reactions of flutter and of fibrillation to special interferences: and the theory as a whole will stand or fall according as it is found to be compatible or incompatible with such reactions. The more complex and varied the reactions, the more searchingly will the main theory be tested. The reactions of flutter and fibrillation to vagal stimulation subject the theory to stringent tests, since the reaction of these states to vagal stimulation is both complex and manifold.

Some of these reactions are already well known, others have been described in insufficient detail. Thus, when the auricles are fibrillating, vagal stimulation usually produces what appears to be a higher grade of disturbance. The auricle, already presenting coarse and irregular twitching movements of its surface, now becomes distended, and very small tremulous movements become visible. These small twitching movements are powerless to move even light lever systems. Coincident with their appearance, the oscillations, ranging in rate from some 400-600 per minute, which characterise the electrocardiogram of fibrillation, disappear and are replaced by much more rapid and smaller oscillations having rates ranging from 1,000 up to 3,000 per minute. This reaction is well known to most observers who have worked at fibrillation of the auricle. For descriptive purposes we shall refer to this condition, in which oscillations of these extreme rates prevail, as the state of *rapid re-oscillation*. The fine tremulous movement of the faradised auricles, under vagal stimulation, was first noticed by McWilliam<sup>6</sup>; the replacement of the usual coarse oscillations of fibrillation by smaller and extremely rapid oscillations in electrocardiograms taken from limb leads in similar circumstances was first described by Rothberger and Winterberg<sup>9</sup> and Lewis.<sup>1</sup> A series of excellent curves depicting this change has been published by Robinson.<sup>8</sup>

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\* Observations undertaken on behalf of the Medical Research Council.

A similar reaction has been recorded in instances where the auricles were originally in a state of flutter, notably by Rothberger and Winterberg in their recent paper.<sup>10</sup> The reaction is in the main responsible for the belief that flutter may be converted into fibrillation by stimulation of the vagus.

But other and curious reactions are seen from time to time. Thus, it has been repeatedly recorded that on occasion fibrillation may be brought to an abrupt termination by vagal stimulation, or that the normal auricular rhythm is restored, after long-continued fibrillation, within a short interval of vagal stimulation (McWilliam,<sup>6</sup> Cushman,<sup>1</sup> Garrey,<sup>3</sup> Robinson<sup>8</sup>). On the other hand it has been reported that stimulation of the vagi (by means of a faradic current, or by drugs known to excite the vagus) may dispose a normally beating auricle to fibrillate without other interference (Winterberg,<sup>11</sup> Cushman<sup>1,2</sup> and Robinson<sup>8</sup>). Fibrillation of the auricles sometimes follows section of the vagi according to Cushman and Garrey. All these reactions, with the exception of the last, have been seen in our present experiments. The apparently contradictory effects have naturally given rise to discussion and to some scepticism. The obvious difficulty of explaining effects, seemingly diametrically opposed, has sometimes led to the belief that many of the rarer sequelæ have been accidental and not brought about by interference with the nerves. We believe them all to be true reactions, and that there is no real incompatibility.\*

Our detailed observations have been confined to the reactions of pure flutter, and the less complex varieties of impure flutter, to vagal stimulation, for these alone have seemed to us capable of satisfactory analysis, and, being analysed, seem to explain sufficiently the similar reactions of the closely allied condition called fibrillation. When the auricles are in flutter (pure or impure) and this state has been continued for periods sufficiently long, vagal stimulation produces changes of three distinct types :—

1. A very gradual and uniform increase of the rate of auricular movement followed, when stimulation ceases, by a decline; the rate falling again to its previous level.

2. The increase of rate just described may be broken into more or less abruptly by the onset of a state of rapid re-excitation, which terminates when vagal stimulation is withdrawn by a gradual return to lower rates. From these lower rates the auricle resumes its former state of flutter or adopts abruptly its normal rhythm.

3. Abrupt cessation of the disorder, followed by an immediate resumption of the normal heart rhythm.

Sometimes even powerful vagal stimulation appears to be without effect on the rhythm of the fluttering auricle.

\* In considering the reports of other writers, it is often difficult or impossible to realise the precise form of auricular disturbance with which they had to deal, owing to its insufficient analysis. Much of the confusion probably arises from this source, and especially from the fact that the temporary state of rapid re-excitation, and the coarser and often much longer continued disorder, have both been termed fibrillation in the past.

### 1. *Gradual increase of rate.*

A gradual acceleration of rate appears to be the commonest reaction of the fluttering auricle to vagal stimulation, but it is not often seen in an uncomplicated form unless the stimulation is weak. It was a reaction emphasised by Rothberger and Winterberg.<sup>10</sup> An example is shown in Fig. 4. The flutter had lasted a minute and three-quarters when the right nerve was stimulated\*: stimulation started as the plate was released and the effect on the ventricle, as the figure shows, was not profound. In the beginning of the curve from lead *II*, the top curve of the figure, the ventricle is seen to be responding to the alternate beats of the auricle: in the later parts of the curve the ventricular action is slower. The remaining curves of the figure were taken from paired contacts placed upon and in line with the tania in the mid-caval region, the top pair lying towards the superior cava and giving curve *S*, and the bottom pair towards the inferior cava and giving curve *I*. The *Z* contact of each pair lay towards the inferior cava: the two being separated by a distance of 8 millimetres. The course of the excitation waves from the superior towards the inferior caval region is indicated by the downward direction of the deflections in the curves from both direct leads and by the slight delay in the appearance of the deflections in the curve (*I*) from the lower contacts. The interval is about 0.01 of a second: so that if we assume the excitation waves to have travelled in the precise line of the contacts, the transmission rate would be about 800 millimetres per second. The regularity of the deflections in form and direction is maintained throughout both curves, but the cycles shorten gradually as the curve proceeds, namely from 0.0943 at the beginning to 0.0871 at the end.<sup>†</sup> In this instance the transmission intervals remain unaltered<sup>‡</sup> throughout the whole curve: these are written below the centre curve. Shortly after the curve was taken, the normal heart rhythm was abruptly resumed. The reaction of acceleration was obtained repeatedly in the same animal, and has been seen repeatedly in other animals (see Protocols). Sometimes the effect can be obtained over and over again during a single period of flutter, the acceleration subsiding and the original form of flutter being resumed.

A second example is shown in Fig. 5, which is very similar to that described. The conditions of this experiment were similar: the two pairs of contacts lay in the mid-caval region and on the line of the tania, but the *Z* contact of each pair was in this instance the upper one. The flutter was not a pure one, as the variation in the lengths of the cycles in the opening

\* The dogs used in the experiments described in this paper were all fully anaesthetised with morphia, paraldehyde and ether throughout the experiments.

† The lengths of the interintrinsic cycles are written immediately above the curves to which they correspond.

‡ Frequently they shorten as the vagus takes effect.

phase of the curve demonstrates.\* The circus movement appears from this curve to have been around one or other cava, it enters the ténia at a point between the two pairs of contacts and spreads in opposite directions over them, upwardly over the top pair, downwardly over the lower pair. The upper pair of contacts is encountered a little before the lower pair. Right vagal stimulation, the onset of which is marked on the curve, slows the ventricle; at the beginning, its responses are to alternate auricular beats, at the end they are to each sixth auricular beat. The auricle, on the contrary, quickens its movements gradually but unmistakably, (the cycles shorten from 0.11 to 0.07 of a second). The curve is thus similar to the last in showing gradual acceleration, though the acceleration is here greater; it differs from the last in that the intervals between corresponding deflections in the two curves change: from small plus values they diminish† to zero, and eventually become minute minus quantities. Coincident with the change of rate there has been a minor change of direction: we say minor, because the forms of the deflections in the two leads do not alter very materially. The chief change to be noticed in the forms of the deflections is that, as the curve proceeds, they become more regular: the impurity of the flutter prevailing before the vagus was stimulated vanishes under that stimulation.

The reason why flutter gradually accelerates under vagal stimulation is not difficult to understand, once the relation of the flutter cycle to the refractory period and transmission rate of the muscle in which it is occurring is fully grasped. In preceding articles of this series it has been shown that, in auricular flutter, the wave, as it circulates, flows through muscle which has not completely recovered its responsive state. The crest of the wave is following very closely upon its own wake. The wave does not flow in as linear a path through the muscle as it otherwise would; its path is more or less sinuous. In frankly impure flutter the sinuosities are often so coarse that direct evidence is obtained of them. In examples of flutter in which the deflections of the electrogram are regular in amplitude and rhythm, the sinuosity of the path is microscopic: it leads, as does the coarser sinuosity, to a decreased rate of propagation from point to point in the auricle. We know from direct observation that excitation waves initiated in sufficiently rapid sequence in the auricle, whether these excitation waves arise from a re-entrant path (as in flutter) or from artificial stimulation at high rates, are propagated slowly: all our evidence goes to show that the slow rate of transmission is brought about by gyrations, which are in turn conditioned by barriers of refractory muscle, of larger or smaller size, standing in the direct path of the wave and deflecting it to one or other side. We also know, in the case of the artificially propagated waves, that vagus stimulation, by reducing the length of the refractory phase, removes these barriers, thus

\* The lengths of the cycles in the upper curve are written vertically above it, those of the lower curve are written horizontally below it, the transmission intervals are written vertically between them; a plus quantity indicates that the upper deflection precedes the lower.

† Simple diminution may be seen without alteration in the form of the deflections.

straightening the course and expediting the rate at which the waves are transmitted. Therefore, in instances of flutter, where the rate of transmission is slow from point to point, vagal stimulation may be anticipated to advance the rate of circulation. To state the matter more generally, if the rate of transmission from point to point in flutter (pure or impure) is lower than it is in the normally beating heart, it is lower because the path along which the wave travels is not clear of obstacles: the rate of transmission will become normal, that is to say it will increase, when by vagal stimulation these obstacles are removed. There is no reason to believe that all the obstacles will be removed at the same instant or that their removal will be abrupt: there is much evidence to show that they will disappear piecemeal.\* *A fortiori*, an abrupt change of rate, is not to be anticipated when vagal

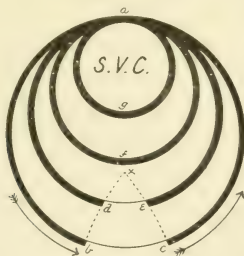


Fig. 1.

A diagram illustrating how flutter may be controlled by the length of the refractory period.

stimulation is relatively weak, or when its observed effect upon the ventricle is a gradually increasing one. It is in these circumstances that the gradual and continued change just described is usually witnessed.

There can be little doubt, therefore, as to the manner in which gradual acceleration of auricular flutter, in response to vagal stimulation, is in many instances brought about. Decreased rates of propagation, however, are not always to be demonstrated in pure flutter, and, in such instances, the explanation which we have given, would not suffice. Gradual acceleration of rate requires a somewhat different explanation in such circumstances.

The second explanation which is adopted to explain why vagal stimulation may produce a gradual and regular acceleration of flutter is illustrated by the accompanying diagram. Three factors are involved in

\* Thus, when the auricle is responding to rapid stimuli, and the rate of transmission is lowered, vagal stimulation does not at once increase the rate of transmission to normal; stimulation must usually be maintained if the full effect is to be observed.

the maintenance of a circus movement, namely, the length of the muscle path, the rate of propagation and the duration of the refractory period. When these three factors are suitably related the excitation wave will pass upon its circular path continuously. Let us suppose in Fig. 1 that the central path chosen by the wave is represented by a uniformly circular path, *abc*, and the factors are such that, at a given instant, the crest of the advancing wave is at *b*, while the effective refractory state is subsiding at *c*. There is a segment (*bc*) of the ring of muscle which at a given moment is in the responsive state. Suppose two factors, namely, the rate of propagation and the length of the refractory period to be constant, but that the central wave were to become deflected into the circular path *ade*, then the segment of responsive muscle lying between the crest (*d*) of the advancing wave and the tail (*e*) of the retreating wave of refractoriness would be shortened. Let the wave be deflected into a still shorter circle (such as *af* or *ag*) and the gap will disappear altogether. It will be clear that in such circles of muscle a circus movement cannot be established. Now suppose that all four circles represent possible paths in a single sheet of muscle, and that all are open to the wave: the wave will pass through all, but its maintenance as a circulating wave will depend, not on the central rings of muscle, but upon the peripheral ones: in the inner rings the crest of the wave will run into muscle which is still refractory and no further progress will be possible, while in the outer rings a gap of varying extent will permit the wave to re-enter. At some point between rings *af* and *abc*, crest and tail will be brought into juxtaposition: in an immediately neighbouring ring of muscle, the shortest re-entrant path will be found. The gap in the rings of muscle taken together will be represented by a wedge *bac*, and the shortest path of re-entry will be across the point of the wedge at *x*. Suppose that such is the condition of affairs during the progress of a given period of flutter and that the wave is circulating around the superior vena cava, and between this vessel and the inferior vena cava. That is a condition which has been observed in experiment. In such a case the rate at which the circuits are completed will be governed by the three factors, the rate of propagation, the duration of the refractory period and by the length of the path through the point *x*. Seeing that in the ring of muscle lying immediately beyond *x* the gap is just open, the length of the path is actually controlled by the duration of the refractory period. Thus, in these circumstances the duration of the cycle is established by two factors, namely, the rate of propagation and the duration of the refractory period. If the flutter is such that the rate of travel is normal, then vagal stimulation will influence the second factor only. The transmission rate remains unchanged: the refractory period becomes shorter. As the refractory period shortens, so the wedge *bac* is driven in, and its point comes to lie first at *f* and then at *g*; the circular paths in which re-entry can be effected become more numerous and shorter paths are opened up. Let the change in the refractory period be a gradual one, and the inevitable result will be a gradual movement of one limb of the



central path from the region of the inferior to the superior cava, a gradual shortening of this path, a gradual shortening of the cycles, and a gradual acceleration of the auricular responses. It is to be concluded then that gradual acceleration of flutter under vagal stimulation may occur in instances of flutter in which the original rate of propagation is normal. We suppose that the wave is circulating in a sheet of muscle around a natural opening, but that before vagal stimulation, the refractory period is of such duration that the opening is not closely encircled,\* that it becomes closely encircled under the influence of nerve stimulation and that, throughout the change, the length of the cycles is governed exclusively by the gradually diminishing refractory period. It is not to be supposed that the superior cava is the only natural orifice around which short circus movements become established; but we use it as our illustration, because it is the opening included in most of the larger circuit movements which have been observed in detail.

Curves, taken from the *tænia* during the period of vagal acceleration, not uncommonly bear witness to a gradual and simultaneous change in the direction which the waves take (see Fig. 5), and this change seems consistent with the hypothesis which we have now discussed.

In principle the second explanation does not differ from that first put forward. Both suppose that quickening of the circus movement is due to shortening of the central path; both assume that this shortening results from a reduced refractory period. The second explanation assumes that the central wave short-circuits a mass of muscle hitherto refractory to the re-entrant wave, the first that it bridges a number of minute refractory barriers: it is believed that both these factors are brought into play, at times singly, at times together.

When we explain the increase in rate as due to the reduction of the refractory period under vagal stimulation, we use the explanation first suggested by Rothberger and Winterberg.<sup>10</sup> In their paper they urge that a reduction of the refractory period may be the cause. But these workers had no direct evidence, such as we have since obtained, that vagal stimulation exerts this influence.† Their paper failed also to explain how the reduction of the refractory period, which is assumed, could produce acceleration of the auricle: it does not concern itself with circus movement, but infers that the impulses spring from a focus.

\* If the openings around which a flutter wave was circulatory, were closely encircled, vagal stimulation might be without effect; the latter is occasionally the case.

† They appear to have relied in the main upon a curve published by Samojloff in which a very conspicuous reduction in the length of the ventricular complex in an electrogram of the frog's ventricle, responding to rhythmic stimulation, is shown under vagal stimulation. Such evidence did not appeal to us as having a sufficiently direct bearing upon our experiments. It has yet to be proved that the ventricular complex is a close guide to the length of the refractory period; and to argue from the frog's ventricle to the dog's auricle seemed to us precarious. Nevertheless, we believe that the explanation put forward by Rothberger and Winterberg is the correct one, in so far as it goes.

The effect of section of the vagus upon auricular flutter has been but little investigated. In six experiments Robinson observed changes in two only, in one of these the auricular rate became considerably slower, in the other the auricular complexes in the electrocardiogram became larger and more distinct. These changes are the expected ones, for they are the reverse of those seen when the vagi are stimulated.

## 2. *Change to a state of rapid re-excitation.*

This, the most remarkable reaction of the fibrillating auricle, is also common in impure flutter, and may occur, though perhaps less frequently, when the auricles exhibit pure flutter. The final mechanism appears to us to be the same, from whatever preliminary state it is induced. The auricle is thrown into a state of feverish activity, accompanied or soon followed by dilatation, which is no doubt enhanced by the simultaneous slowing or standstill of the ventricle. On the surface very minute twitching movements of extremely rapid rate are visible: the electrocardiograms of limb leads shows a conspicuous change, the large auricular complexes or coarse oscillations give place to finer oscillations of much higher rate and of smaller amplitude. The curves of direct leads have been well described by Rothberger and Winterberg: very rapid deflections, of considerable amplitude—an amplitude not necessarily less but sometimes greater than those of the more slowly beating auricle—are seen.

In rate they vary up to 3,000 per minute, and often follow each other at seemingly regular intervals, and may be of almost, though not quite, uniform amplitude for many successive cycles. Fine measurement shows that they are not quite uniform in sequence for more than a few cycles together, this irregularity going hand in hand with changes in excursion, form and even direction. The state does not at once fully establish itself, but it develops quickly. As Rothberger and Winterberg point out, the full rate subsides gradually after vagal stimulation is withdrawn: eventually it falls within some seconds or a few minutes to 500 or 400 or even less per minute.\* Flutter or fibrillation, according to the preceding events, or normal rhythm, may then be resumed.

The full state of rapid re-excitation appears to be identical with or very similar to the local mechanism set up in the unatropinised auricle where it is submitted to faradic stimulation, a local state which has been described fully in an earlier article of this series.

The *first example* is shown in Fig. 6. The top curve is an electrocardiogram from lead *II*, the curves *I* and *S* are from paired contacts placed in the line of the tænia terminalis in the mid-caval region. The arrangement of the contacts is shown in the corresponding diagram, Fig. 2, *S* representing the contacts placed nearest the superior and *I* those placed

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\* In Rothberger and Winterberg's experiments, the animals were poisoned with physostigmin or muscarine, and the condition was consequently of much longer duration. As to its longer duration under physostigmin we are able fully to confirm these writers.



nearest the inferior vena cava. The right vagus was faradised shortly after the commencement of the plate, and during a period of slightly impure flutter which had lasted for one half-minute. Certain deflections of Fig. 6 are lettered, and these are charted in Fig. 2. The flutter rate was 583 per minute before vagal stimulation, and the excitation waves were passing up the tænia over both pairs of contacts, as is indicated by the direction of the deflections and their relation to each other in the two direct leads. Vagal stimulation, which was strong, began just before the first charted deflection (*a*) and continued throughout the plate. For three cycles the rate remains unchanged; the first change comes at cycle *e*, which is slightly premature. A little further acceleration is shown during the next few cycles (up to deflection *l*) the rate rising to 718 per minute (as calculated from cycle *kl*); but up to this point, although the deflections exhibit a slightly increased variation in amplitude there is no change in form or sign, nor is there change in the transmission intervals. This slight and gradual change of rate is similar to that already described in detail, and is ascribed to the causes there discussed. At cycle *m* there is a more conspicuous change, at this point the upwardly coursing wave which is expected passes across the lower contacts, but a premature wave flowing in the opposite direction strikes the upper contacts at almost the same instant. The wave of cycle *n* is still more premature and flows over both contacts from above downwards, the reversed interval being of similar magnitude to the original values. There follows a cycle (*no*) of increased length which almost exactly compensates for the previous disturbance; and a movement similar to the original one, but of rapidly advancing rate, is resumed until near the end of the curve, when reversal is again seen and is maintained (deflection *y* and *z*, etc.). From *l* to *g* there is a very rapid increase of rate which rises at the end of the plate to about 1,300 per minute (as calculated from cycle *yz*). Our interpretation of these events is as follows. At *m*, a barrier of hitherto refractory muscle is removed for one or more cycles, and there is an attempt of the excitation wave to establish a new and shorter circuit. The wave of new direction meets the next regular wave for one cycle under the contacts, at the next a little past the contacts: it is unable to establish itself and the original circus movement continues at an increasing rate as its path shortens. The original path shortens further until again a new and quicker path is found at *y*, a path similar to that followed at *m*. On this occasion the new path is followed for many cycles, and the new circus becomes established. All these changes are attributable to a progressive reduction of the refractory period of the muscle, consequent upon vagal stimulation. The lack of precise uniformity of the events is to be ascribed to the conflict of the excitation waves for two re-entrant paths, one the shortened original path, the other a new one.

The *second example* is from another animal. The right vagus was stimulated by means of rapid rhythmic shocks during an impure flutter which had lasted four minutes. These shocks are visible upon and disturb the curve taken from lead *II* (Fig. 7). Right vagal stimulation started at the

beginning of this record. The corresponding chart and a diagram of the contacts from which the electrograms were taken is shown in Fig. 3. The two pairs of contacts lay on the tænia terminalis and in line with it, one pair (*S*) lying towards the superior vena cava and the other (*I*) towards the inferior cava. The movement of the excitation wave, when this curve opens, is indicated by the direction of the deflections, and by the time relations of corresponding deflections in the two leads: it is shown to be up the tænia. The full effect of vagal stimulation is delayed. Over the early part of the curve, namely, between deflection *a* to *k*, there is slight quickening of rate, otherwise there is no change: the deflections continue to vary a little in amplitude: the transmission intervals vary a little, but otherwise remain unaltered in sign. At deflection *l* the almost regular movement of the excitation waves up the tænia is disturbed. The expected deflection is found in the curve from the contacts nearest the inferior cava, but the same wave has now found a shorter path to the upper contacts and crosses them from above downwards to meet the ascending wave. From this point onwards the waves pass uniformly from above downwards over all four contacts: the directions of the deflections are now all opposite to what they were originally, and the transmission intervals have reversed signs. Within a period of a second the rate doubles. The analysis is taken as far as deflections *y*, at which instant the rate is approximately 1,200 per minute. From this point onwards the deflections of Fig. 7 lose much of the regularity of form, amplitude and incidence which they at first possessed, and a very rapid and more irregular movement sets in. It occurs at a period slightly preceding that at which the vagus appears, from the lengthened inter-ventricular intervals of lead *II*, to be exerting its maximal effect on the heart.

The curve is interpreted upon similar lines to the first example. The initial quickening, slight but definite, is supposed to result from shortening of the original central path: when the direction of the deflections changes it is supposed that a new and shorter central path becomes established, presumably in the body of the right auricle, rather than around a cava.

The curves, of which these are examples, are very variable in form, though the main features described are constant. An initial slight quickening is the rule, though it may be less in degree than these two illustrations indicate: it is often of much shorter duration, and the onset of the rapid re-excitations is more abrupt: in such curves there may be no further quickening of the waves, the waves appearing at once at the full rate of 2,500 or 3,000 per minute. These examples are seen when the vagus exerts a more sudden effect on the heart, bringing the ventricle to an almost immediate standstill. They are usually less adapted to clear analysis than those we publish. Usually the curves show simultaneous though contrary changes in the rates of the auricular oscillations and in those of the ventricle. This relation is not quite constant, however.

The difference between the two effects of vagal stimulation, which have now been described, is one of degree rather than of kind: the basal

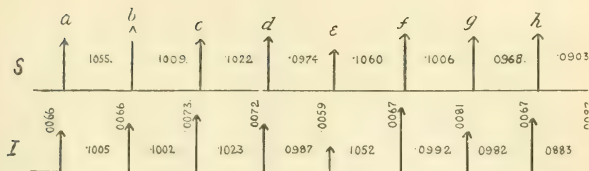


Fig. 2. *Dog LI. (Record 3.)* The arrangement of leading off contacts is shown to the right of terminals. The chart analyses the lettered portion of Fig. 6. The two series of curves show whether it was an upstroke or downstroke in the curve; the direction of the arrow indicates the direction of the wave. If an excitation wave strikes Z first it yields an upstroke; if C first it yields a downstroke. The intervals between corresponding deflections of the two curves are written vertically,

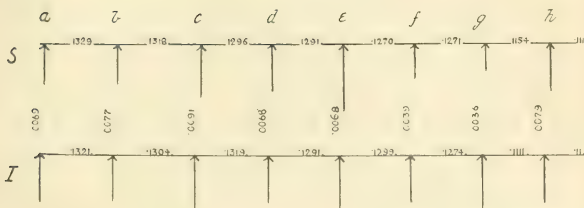
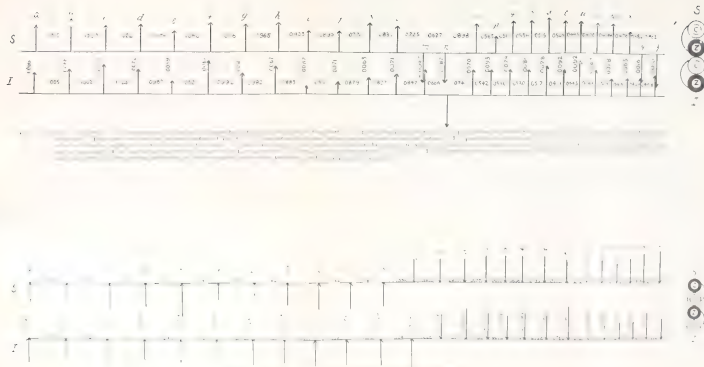


Fig. 3. *Dog LG. (Record 6.)*



phenomenon is a reduced refractory period. Where the reduction is gradual and the auricular cycles are influenced by it, the acceleration is gradual: but as the refractory period is further reduced, a time may come when a new and much shorter path becomes open to the wave, and the rate then springs up more abruptly.\*

The ending of the state of rapid re-excitation is not unlike its beginning, though a gradual and more uniform change of rate is the rule. The decline in rate begins shortly after stimulation ends. When the rate falls sufficiently, a flutter, similar to that prevailing originally, may be resumed, though more commonly the abnormal mechanism ends, and the normal rhythm returns abruptly.

The state of rapid re-excitation is one of considerable interest and importance from a theoretical standpoint. For some while we have pursued a further investigation of it: to describe these observations would prolong this paper to an undesirable length. We purpose to return to the subject at a somewhat later date, being content for the moment to record the following observations and conclusions.†

The state of rapid re-excitation may be induced regularly and without fail if, under vagal stimulation, two successive break shocks enter the muscle at a critical time relative to each other. It may be produced by stimulating the auricle rhythmically, and subsequently stimulating the vagus: this method is less certain than the last, but becomes more certain as the rate of the rhythmic shocks is increased. The reaction is rarely seen unless the rate of rhythmic stimulation is equal to the rates which prevail in flutter: this observation is important in that it shows that the abrupt onset of rapid re-excitation is not a peculiarity of the fluttering or fibrillating auricle, but may be brought about by vagal stimulation when the auricle is responding at a high rate, whether to a circulating wave or to rhythmic shocks seems a matter of indifference. On very rare occasions the auricle is thrown into this state from its normal rhythm by exciting the vagus: it is this occasional reaction which is probably responsible for the statement that the normal rhythm may be converted into fibrillation by vagal stimulation.

The rapid waves are conveyed as single waves over the whole surface of the auricle, the state of rapid re-excitation is to this extent co-ordinate: they often appear to be conveyed at transmission rates which are not materially lower than those prevailing when the auricle beats slowly. We have proof that under vagal stimulation excitation waves are conveyed quite normally up to rates of 800 or 1,100 per minute.

Our observations go to show that the state of rapid re-excitation in the auricle under strong vagus influence is comparable to flutter (pure and impure) in the uninfluenced auricle: the state of rapid re-excitation is equivalent to flutter on a diminutive scale, the last conditioned by the great reduction of the refractory period which occurs under vagal stimulation.

Our evidence for these statements will be given in full in a future article.

\* The very rapid movement is not due as McWilliam<sup>7</sup> has supposed to disturbed conductivity and inter-fascicular block. The vagus has no effect on auricular conductivity (meaning fibre conductivity).

† See Proc. physiol. Soc., Jan. 22, 1921.

### 3. *Abrupt cessation of flutter.*

It should be stated first of all that of this form of reaction there is no doubt. Naturally, when flutter after-effects are of short duration, a spontaneous termination may coincide, as a matter of chance, with the period of vagal stimulation. That the association is not fortuitous is clear when, repeatedly in the same animal or in different animals, long continued flutter is quickly brought to an end by this interference (see Protocols). The reaction is unquestionable, but occurs for the most part under weak stimulation or at the very beginning of a stronger stimulation. When we first witnessed the effect, we were tempted to ascribe it to depressed conduction in the auricle, whereby the continued progress of circus movement was prevented. Investigation of transmission rates in the auricle in and out of vagal stimulation soon demonstrates this view to be untenable. To explain the abrupt ending of flutter and a resumption of the normal heart rhythm as a consequence of vagal stimulation, we hark back to the interpretation of gradual acceleration.

Consider an auricle which is in a state of flutter: suppose the excitation wave to be moving along a circular path and the rate of movement to be below normal. This reduced rate is not the consequence of a reduced power of the individual fibres to conduct, but to many fibres being still refractory when the wave re-enters. In its course, the wave sways from side to side upon a sinuous course, being deflected by innumerable small barriers. Suppose further, as we must suppose, that a short gap of partially responsive muscle exists between the crest of the wave as it travels and the wake of absolute refractoriness, which it follows. What now may be the effects of vagal stimulation? The small barriers are gradually removed and the cycles shorten: the flutter accelerates and the crest of the wave is brought nearer to the wake of absolutely refractory muscle. If the transmission rate is by this means sufficiently increased, *the gap may disappear* and the oncoming wave will find before it no responsive tissue to re-enter. It is quite clear that circus movement can be maintained only if the time taken for the circuit to be completed is greater than the duration of the absolute refractory period: there must be a gap. Now a reduction of the refractory period, in the circumstances of the flutter which we are considering, will have, sooner or later, opposing effects upon this gap. Removal of the small barriers will decrease the duration of the cycle and tend to close the gap: general reduction of the absolute refractory period will tend to widen the gap. If these two processes occur simultaneously and exert equal though opposite effects upon the gap, the circus movement will continue at an ever increasing rate. But if, in the initial stages of stimulation, the removal of small barriers expedites the passage of the wave, thus shortening the gap to an extent largely in excess of its lengthening by general reduction of the absolute refractory period, the gap will disappear. It is known that the rate of travel from point to point in flutter may be twice as slow as it is normally, and that vagal stimulation will

restore the normal speed. When this change happens, the circus movement must come abruptly to an end, unless on the one hand a path of re-entry twice the original length is open to it, or on the other hand the absolute refractory period reduced in the muscle generally by an equal time period. Probably flutter of the kind considered is usually maintained in the early stages of vagal stimulation by a combination of these changes. But, when we consider fully the circumstances, there seems insufficient reason to anticipate that the opposing influences will always so balance that the gap remains or widens; on the contrary, there is reason to anticipate that the gap will sometimes vanish, thus bringing the flutter to an end.

If the views here expressed are tenable, we should expect to see in records of the ending, an initial quickening of rate, and, finally, variable events. In some instances the actual termination should come quite abruptly, the potential overlap being extensive; in other instances we might anticipate an irregular action as the waves struggle for re-entrant paths; in yet other curves we should anticipate evidence of a change in the direction of the waves as the circuit widens out to escape refractory barriers. Each of these disturbances is actually evidenced by the curves, of which we now proceed to show examples.

*Examples.* Curves which show the resumption of normal rhythm under vagal stimulation vary a good deal in detail. An example which presents a number of the usual features is shown in Fig. 8. The top curve was taken from lead *II*, the lower curves were taken from direct leads. The four contacts lay on and in line with the tænia, an upper pair (*S*) towards the superior and a lower pair (*I*) towards the inferior cava. The *Z* contact of each pair lay towards the superior cava. A slightly impure flutter had been in progress for a minute and a half: the course of the circulating wave was down the tænia terminidis. The curve starts at the moment when a weak current was thrown into the right vagus.

At the beginning the flutter is showing regular alternation, which is most conspicuous in curve *S*: this gives place to a slighter and less regular disturbance towards the end. Over the first half of the curve the rate of flutter is seen to quicken gradually and steadily: but this quickening, unlike that of Fig. 5, is not continued throughout: towards the end of the flutter the lengths of the last few cycles are irregular, but they are not further reduced. It is presumed that the check to the rising rate happens when the gap between the crest and wake of the circulating wave is all but filled, and that the irregularity in the lengths of the cycles speaks of the struggle to find a path of re-entry. The last flutter deflection shown is of unusual form and reversed direction, and occurs after an unusual delay. At the beginning of the curve the excitation waves flowed down the line of the tænia, striking the *Z* contact of each pair first, and the *Z* contact of the upper pair (*S*) before the *Z* contact of the lower (*I*) by intervals of 0.0143 and 0.0162 of a second: during the last cycle the *C* contact of each pair is first encountered



and the *C* contact of the lower pair (*I*) is reached slightly before the corresponding contact of the upper pair, though by a much reduced interval. The last excitation wave flowing over the contacts has not followed their precise line, but has struck them from the side. To reach the contacts from the side this excitation wave has made a detour, and it comes to them delayed. Had this delay been a little greater the flutter would have ended at the previous cycle.

A little delay of the last cycle is frequent in the curves, though it is not constant. The relations appear to be similar to those found when the auricle is responding to very rapid rhythmic stimuli, and breaks into a 2:1 response (as described on page 117 in the preceding article of this series). Before the break, a cycle of 1:1 response of unusual length is frequent, and it is produced by delay of the last excitation wave. This delay has been attributed to the wave running into tissue which has only very partially recovered its responsiveness, and the same explanation applies here. According to the degree of recovery, the wave proceeds slowly or fails to proceed.

A not dissimilar example is shown in the second record (Fig. 9) taken in very similar circumstances from another animal and 45 seconds after the onset of flutter. The two curves are from direct tænia leads, the upper from the region of the superior cava (*S*) the lower from the region of the mid-cava (*I*). Right vagal stimulation began as the plate started to record. The excitation waves in this case were preceding up the tænia. The rate of the auricular movement shows the usual gradual increase, up to a point within four cycles of the actual ending. At this point acceleration ends and the cycles become irregular in length, the last two waves showing altered direction. Simultaneously with the increase of rate, the transmission intervals decrease; the last interval (0.0056) is unusually short.

A more speedy ending in another animal is shown in Fig. 10. This form is exceptional for its abruptness and for the slight degree of preliminary change. The top curve is from lead *II*. The two lower curves were taken from direct leads, the contacts being in the line of the tænia, a pair (*S*) lying towards the superior and a pair (*I*) towards the inferior cava. The *Z* contact was above in each pair, and the deflections show the excitation waves to be flowing up the tænia. The flutter had been in progress for a little more than a minute when the left vagus was stimulated. There is little or no preliminary increase of rate. The chief change is that the deflections alter their amplitudes; whereas, before vagal stimulation begins and for a few cycles afterwards, these deflections alternate in depth, the last few deflections vary in amplitude in a more irregular way.

It is noteworthy that vagal stimulation may increase or decrease the impurity of flutter. When there is a gradual and continued acceleration, such as is illustrated in Fig. 4 and 5, any original irregularity in the amplitude and spacing of the deflections tends to disappear. This speaks for a widening of the gap between the crest and wake of the waves as they travel, whereby these waves enter muscle in a more completely responsive state. When the



acceleration is leading up to termination of the flutter, as in the examples now described, these irregularities do not disappear: on the contrary, they frequently increase in magnitude, indicating that the gap is closing up, and that the crest of the wave is entering tissue in which recovery is less advanced. This stage is the critical one: a little more closure and the oncoming wave is unable to proceed and the flutter terminates.

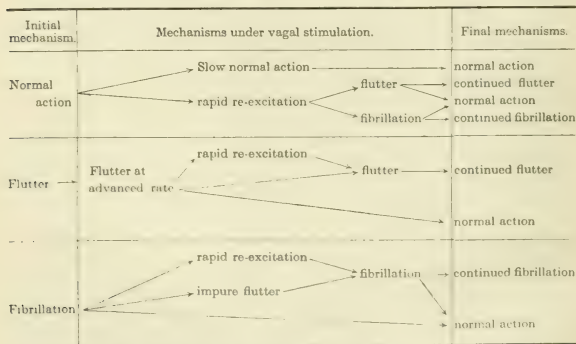
### *Discussion.*

It has been shown that if the auricles are fluttering, vagal stimulation will sometimes induce a high grade of auricular disorder, here termed rapid re-excitation, but hitherto included in the term fibrillation. It is known that a similar form of incoordination is induced by faradic stimulation of the auricle, and that this effect is more certain, and the high grade of incoordination of longer duration, when the faradic stimulation of the muscle is combined with vagal stimulation. On occasion vagal stimulation alone will throw the naturally beating auricle into a state of rapid re-excitation. In subsiding, rapid re-excitation may set up a regular or irregular circus movement (flutter or fibrillation). These facts have led to the general statements that vagal stimulation predisposes to or will induce auricular fibrillation, and that it will convert flutter into fibrillation.<sup>5,10</sup>

It is also true that vagal stimulation will sometimes bring flutter or fibrillation to an end, and the two series of observations have stood hitherto in apparent contradiction. They are not in reality contradictory. When the auricle is beating in response to a stimulating current, or is in a state of flutter, vagal stimulation reduces the refractory period and excites that rapid re-excitation of the tissue, which we interpret as the result of re-entrant waves. This state of rapid re-excitation becomes slower as the vagal influences fade away and the auricular tissue displays a series of transitional mechanisms as its rate of beating slows, some of which at all events are properly included in the term fibrillation. The actual end effect is variable, according to the circumstances: the normal rhythm may be resumed abruptly, or if the original condition was one of flutter or fibrillation, either of these last two mechanisms may reappear and become established. These end effects are not the end effects of vagal stimulation, but they are the end effects of the state of rapid re-excitation. Throw the auricle or a portion of it into this state and it will subside when its provoking cause, namely, reduced refractory period under vagal stimulation is removed. Sooner or later there is a change to a different mechanism in different animals or in different observations upon the same animal: the change is to normal rhythm, flutter or fibrillation, according to the predisposition of the auricle under observation and according to the establishment or otherwise of large re-entering circuits. If the auricle is fibrillating originally when the vagus is stimulated, this fibrillation is wiped out by the state of rapid excitation;

but as this passes away the original state of fibrillation may appear as an after-effect: if it is not provoked, the normal rhythm will appear. If the auricle is fluttering originally, vagus stimulation may throw it into a state of rapid re-excitation: this when it subsides may leave no after-effect, the heart suddenly beginning to beat normally, or it induces a more or less persistent condition, a flutter resembling the original flutter or a state of less pure flutter. There is no more contradiction in these observations than there is in the well known fact that simple faradisation of the auricle produces an after effect on one occasion, and on the next occasion produces none; the variable end result depends both in faradisation of the auricle and in faradisation of the vagus, while the auricles are beating rapidly, upon the chance of a relatively large circus movement becoming established as the state of rapid re-excitation subsides.

*Chief effects of vagal stimulation on the auricle*



In large part, though not entirely, the apparent contradictions which have been reported are thus explained. Two further reactions are still to be considered. First, an auricle which is beating normally may on very rare occasions be thrown by vagal stimulation into flutter or fibrillation. This reaction is not dissimilar to those already described, for the rise of vagal tone throws the auricle primarily into a state of rapid re-excitation. Secondly, stimulation of the vagus during the progress of flutter may bring the latter to an abrupt ending, without the interposition of the state of rapid re-excitation. This also receives its explanation: it is due, so it would appear, to the manner in which the refractory period is reduced, and to the opposing effects of this reduction upon the length of the essential gap of responsive

muscle which exists between the crest and wake of the circulating wave ; this gap may enlarge or it may decrease. The explanation is adequate in the case of flutter, it would seem equally adequate in the case of fibrillation, for the last is also brought on occasion to an abrupt end by vagal stimulation, without the intervention of the state of rapid re-excitation.

Other occasional reactions are also brought into line. When the auricles are fibrillating, vagal stimulation will sometimes bring them into a state more closely resembling flutter : when this happens it is to be supposed that the gap between crest and wake is increased, whereby the progress of the re-entrant wave becomes more uniform. When the auricles are fluttering, vagal stimulation may cause this flutter to become impure, or on rare occasions convert it temporarily to a state closely approaching fibrillation : when this happens, it is probable that the gap between the crest and wake of the waves has been shortened, whereby the course of the re-entrant wave is rendered more sinuous.

#### SUMMARY.

A state of rapid re-excitation, identical with that resulting locally from faradisation of the auricle, is often induced in the auricle by vagal stimulation when the auricles are previously fluttering or fibrillating, and may be induced occasionally by vagal stimulation when the auricles are beating normally. This state of rapid re-excitation subsides as the vagal influence is withdrawn ; the after-effects are the same as those which follow rapid re-excitation induced locally by faradising the auricle : there may be no after-effect, in which case the normal rhythm is resumed, or the after-effect may be constituted by flutter or fibrillation according to the predisposition of the auricle.

Vagus stimulation exerts opposing influences upon the length of the gap between the crest and wake of the circulating wave. When it shortens the gap, the circulating wave takes a more irregular course and, if the gap is reduced to zero, the circus movement is brought to an end : when the gap widens, the circus movement tends to become more regular. Both these reactions are customarily associated with an advance in the rate at which the auricle beats.

All these reactions are primarily attributed to a reduction of the refractory period consequent on vagal stimulation.

The relations of flutter and fibrillation to vagal tone are complex, the reactions of the auricle to vagal stimulation manifold and at first seemingly contradictory. But as the factors underlying these reactions are investigated in detail, so the variable after-effects of vagal stimulation become clear. They become clear because the theory that flutter and fibrillation are essentially circus movements, a fundamental assumption in explaining these reactions, is sound. Thus the study of flutter and fibrillation, in its relation to the vagus, brings powerful support to our main thesis.

## PROTOCOLS.

(Exemplifying the action of the vagi upon flutter.)

(R.V. and L.V. = right or left vagus stimulated; I.R. = increased rate of flutter; R.Re. = rapid re-excitation appears; N.R. = normal rhythm resumed; F.R. = flutter resumed.)

*Dog L.D.* 1. Slightly impure flutter; L.V. at 45 seconds; *effect*, I.R., conversion into auricular fibrillation, F.R.; spontaneously ending at 3½ minutes.2. Slightly impure flutter; L.V. at 1 minute; *effect*, abrupt N.R. The vagal stimulation was weak.*Dog L.F.* This animal showed long after-effects of rhythmic stimulation which consisted of slightly impure flutter. Vagal stimulation weak.

1. Flutter; R.V. at 5 minutes and at 6½ minutes; no apparent effect; spontaneous ending at 11 minutes.

2. Flutter; R.V. at 4 minutes; *effect*, I.R., R.Re., N.R.3. Flutter; R.V. at 2½ minutes; *effect*, I.R., R.Re., F.R., spontaneous ending at 8 minutes.4. Flutter; R.V. at 1 minute; *effect*, I.R., R.Re., N.R.5. Flutter; R.V. at 45 seconds; *effect*, I.R., N.R.6. Flutter; R.V. at 1 minute; *effect*, I.R., N.R.7. Flutter; R.V. at 30 seconds; *effect*, I.R., F.R.; R.V. at 4 minutes; *effect*, I.R., F.R.; R.V. at 8 minutes; *effect*, I.R., F.R.; spontaneous ending at 10 minutes.8. Flutter; L.V. at 45 seconds; *effect*, I.R., F.R.; L.V. at 4 minutes; *effect*, I.R., F.R.; L.V. at 6 minutes; *effect*, I.R., F.R.; L.V. at 7½ minutes; *effect*, I.R., F.R.; L.V. at 12½ minutes; *effect*, I.R., F.R.; R.V. at 15 minutes; *effect*, I.R., N.R.*Dog L.G.* This animal showed after-effects of rhythmic stimulation, consisting of pure or slightly impure flutter. The vagal stimulation was weak.1. Flutter; R.V. at 4 minutes; *effect*, I.R., R.Re., N.R.2-5. Flutter; R.V. at 1½ minutes; *effect*, I.R., N.R.; repeated three more times.6. Flutter; L.V. at 55 seconds; *effect*, I.R., F.R.; L.V. at 3 minutes; *effect*, I.R., N.R.7-9. Flutter; R.V. at 1½ minutes; *effect*, I.R., N.R. Repeated twice.10. Flutter; R.V. at 70 seconds; *effect*, I.R., F.R.; R.V. at 4 minutes 10 seconds; *effect*, I.R., N.R.*Dog L.J.* This animal showed after-effects of rhythmic stimulation consisting of pure or slightly impure flutter. The vagal stimulation was moderately strong.1. Flutter; R.V. at 45 seconds; *effect*, I.R., N.R.2. Flutter; R.V. at 20 seconds; *effect*, I.R., R.Re., F.R.; R.V. at 2 minutes; *effect*, I.R., R.Re., F.R.; R.V. at 3½ minutes; *effect*, I.R., R.Re., F.R.; R.V. at 4½ minutes; *effect*, R.Re., N.R.3. Flutter; R.V. at 1 minute; *effect*, I.R., F.R. Spontaneous ending at 39 minutes.*Dog L.K.* This animal showed after-effects of rhythmic stimulation consisting of impure flutter. The vagal stimulation was moderately strong.1. Flutter; R.V. at 2 minutes; *effect*, R.Re., N.R.2. Flutter; R.V. at 25 seconds; *effect*, R.Re., F.R.; R.V. at 1½ minutes; *effect*, R.Re., F.R.; R.V. at 4 minutes; *effect*, R.Re., F.R.; R.V. at 5 minutes; *effect*, R.Re., F.R.; R.V. at 6 minutes; *effect*, R.Re., N.R.3. Flutter; L.V. at 1½ minutes; *effect*, I.R., N.R.4. Flutter; L.V. at 2 minutes; *effect*, R.Re., N.R.5-15. Flutter; R.V. at 2 minutes; *effect*, R.Re., N.R. Same repeated 10 times after flutter had lasted, respectively, 1 minute, 2 seconds, 5 seconds, 10 seconds, 10 seconds, 2 seconds, 2 seconds, 1 minute, 1 minute, 1 minute.16. Flutter; L.V. at 1 minute; *effect*, R.Re., N.R.17. Flutter; L.V. at 1 minute; *effect*, R.Re., F.R.; L.V. at 1½ minutes; *effect*, R.Re., F.R.; L.V. at 2½ minutes; *effect*, R.Re., F.R.; R.V. at 3½ minutes; *effect*, R.Re., N.R.18. Flutter; R.V. at 10 seconds; *effect*, R.Re., N.R.19. Flutter; R.V. at 1 minute; *effect*, R.Re., N.R.20. Flutter; R.V. at 1 minute; *effect*, R.Re., F.R. Ended spontaneously.

*Dog I.L.* This animal showed after-effects of rhythmic stimulation consisting of impure flutter. The vagal stimulation was moderately strong.

1. Flutter; R.V. at 1 minute; *effect*, I.R., R.Re., N.R.
2. Flutter; R.V. at 15 seconds; *effect*, I.R., N.R.
3. Flutter; R.V. at 10 seconds; *effect*, I.R., N.R.; spontaneous flutter; R.V. at 3 minutes *effect*, N.R.

*Dog I.M.* This animal showed after-effects of rhythmic stimulation consisting of slightly impure flutter. The vagal stimulation was strong.

1. Flutter; R.V. at 2 minutes; *effect*, I.R., N.R.
2. Flutter; R.V. at 45 seconds; I.R., F.R. Ended spontaneously at 1½ minutes.
3. Flutter; R.V. at 1 minute; *effect*, I.R., N.R.

*Dog M.A.* 1. Slightly impure flutter; R.V. at 1½ minutes; *effect*, I.R., R.Re., N.R.

2. Slightly impure flutter; R.V. at 15 seconds; *effect* I.R., N.R. The vagal stimulation was weak.

*Dog L.L.* This animal showed after-effects of rhythmic stimulation consisting of pure flutter. The vagal stimulation was weak.

- 1-5. Flutter; R.V. at 1 minute; *effect*, I.R., R.Re., N.R. Repeated 5 times.
7. Flutter; R.V. at 1 minute; *effect*, I.R., N.R.
- 8-12. Flutter; R.V. at 1 minute; *effect*, I.R., R.Re., N.R. Repeated 3 times.

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- <sup>5</sup> McWILLIAM. Journ. of Physiol., 1887, viii, 296.
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- <sup>9</sup> ROTHBERGER AND WINTERBERG. Archiv. f. d. ges. Physiol., 1910, cxxxi, 387.
- <sup>10</sup> ROTHBERGER AND WINTERBERG. Archiv. f. d. ges. Physiol., 1914-5, clx, 42.
- <sup>11</sup> WINTERBERG. Archiv. f. d. ges. Physiol., 1908, cxxii, 361.



In the following records, the standard of the electrocardiograms was 1 centimetre 1 millivolt, and of the electrograms approximately 1 centimetre = 3 millivolts.

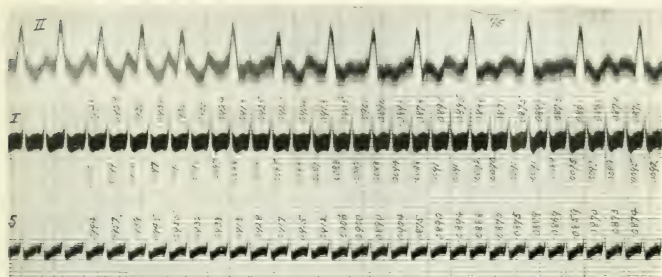


Fig. 4. *Dog L.J.* (Record 6). Simultaneous curves from lead II and from two direct auricular leads. The two direct leads were from two pairs of contacts placed in line on the tenia terminalis. I is a curve from the contacts towards inferior and S from those towards the superior vena cava. The Z contact of each pair lay towards the inferior vena, the two being 5 millimetres apart. The lengths of cycles are written above the cycles to which they corresponded, the transmission intervals between curves I and S, in seconds.

Showing the accelerating effect of right vagal stimulation upon auricular flutter. Time lines in tenths and fifths of a second in all figures.

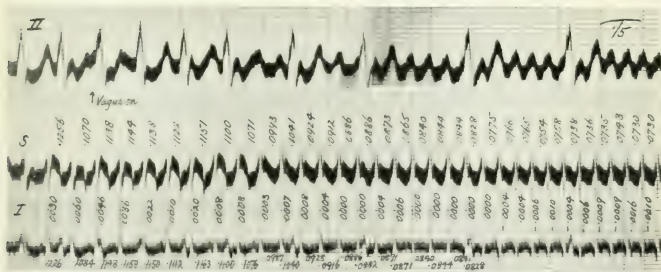


Fig. 5. *Dog L.J.* (Record 6). Similar curves to the last. The contacts were similarly placed on the tenia, except that in this instance the two Z contacts lay towards the superior vena cava. The lengths of the cycles are written above and below and the transmission intervals between the two electrograms.

Showing the accelerating effect of right vagal stimulation on auricular flutter and a change in the transmission intervals. The ventricle (see lead I I) is retarded.







Fig. 6. Dog L1. (Record 3.) Curves taken similarly to those previously described. The arrangement of contacts and an analysis of the lettered deflections are shown in Fig. 2.

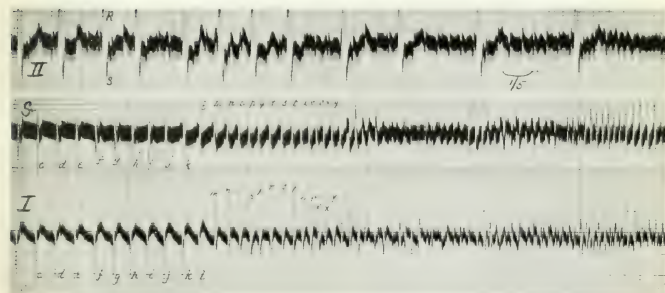
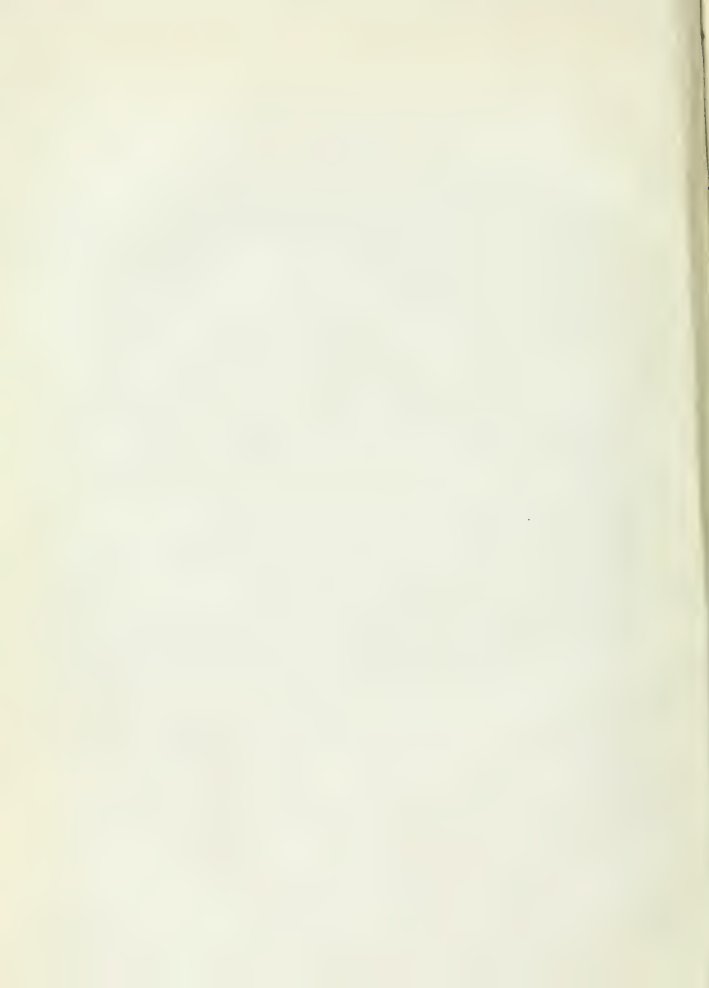


Fig. 7. Dog LG. (Record 6.) Similar curves to the last. The arrangement of contacts and an analysis of the lettered deflections are shown in Fig. 3.

Showing an acceleration of flutter and the production of rapid re-excitation under right vagal stimulation.







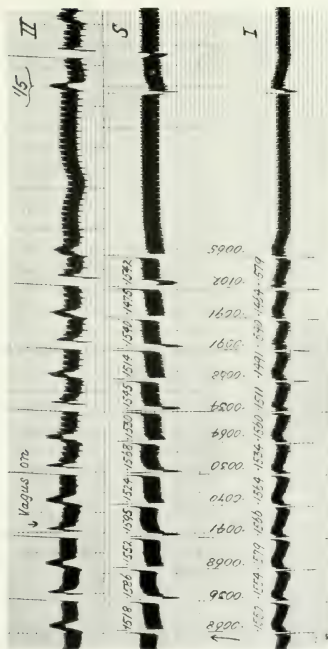


Fig. 10. Dog I.D., a second 17.) Curves taken similarly to those of Fig. 8. The Z contacts of both pairs lay towards the superior cavity. Showing an abrupt termination of flutter under weak stimulation of the left vagus.



## OBSERVATIONS UPON FLUTTER AND FIBRILLATION.

### PART VIII. —THE ELECTROCARDIOGRAMS OF CLINICAL FIBRILLATION.\*

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THE electrocardiographic curves, obtained by limb-leads from clinical cases of auricular fibrillation, have been extensively studied during recent years. The form and features of such curves are well known. They are comprised of ventricular and auricular electrical effects. The latter consist of oscillations which have an irregular incidence and amplitude. Usually two distinct auricular phases are to be found. These phases merge imperceptibly one into the other, and are characterised by fine rapid oscillations or absence of movement in one, and coarse oscillations in the other. The coarse oscillations are of all amplitudes up to and exceeding that of the usual *P* wave and vary in incidence and form. These two phases alternate in some cases in an irregularly periodic manner, or to express the matter differently, the oscillations wax and wane from time to time. In many cases, however, little or no trace of the coarse oscillations can be found; while, in a few, they appear continuously over long stretches of curve. The phases of oscillation appear more frequently and prominently in lead *II* or lead *III* rather than in lead *I*.

Both the coarse and the fine rapid oscillations have been ascribed to auricular movement, and have been used in calculating the rate of the general movement of the auricle. Such calculations, based on a study of the oscillations in curves taken from limb leads, are necessarily precarious, owing to the imperfections of these leads. The curves so obtained are distorted in greater or less degree by irregularities caused by minor movements of the patient during examination, and in those patients who are obviously tremulous this distortion cannot be eliminated. Tremor of the somatic muscle, obvious or less obvious, may not only confuse the large oscillations which are periodically present, but may itself give rise to a series of fine rapid oscillations in the curve. It is necessary, therefore, before any evidence

\* Observations undertaken on behalf of the Medical Research Council.

can be adduced from limb leads with regard to auricular activity, that they should be checked by simultaneous curves taken by other means which eliminate, as far as possible, their imperfections.

The present investigation is an attempt to define the limitations of limb leads as indicative of auricular activity, to arrive at the meaning of the phasic character of the oscillations, and, if possible, to assign a mechanism to the auricular movement which is compatible with the presence of these coarse oscillations, which form the chief characteristic of the electrocardiograms in clinical fibrillation.

Previous work has shown that these prominent oscillations arise in the vicinity of the auricle, consequently we have used the method of leading from the chest in studying them.

*Method.* The method adopted was that used by Lewis,<sup>2</sup> and consists of attaching to the front or to the back of the chest copper discs, about 1½ inches in diameter, by means of a stiff paste of flour, salt and water. Two copper discs are connected in circuit with a galvanometer in the usual way.

The position of such paired contacts has varied in some degree, but has usually approximated to two general positions. One position used has been the front of the chest (sternal lead); the Z contact is fixed at the junction of the 2nd right rib with the sternum and the C contact at the 7th right costal cartilage. The other position used has been the front and the back of the chest (antero-posterior lead): the Z contact is placed at the mid-point of the sternum, and the C contact at the level of the angle of the right scapula, 2 inches to the right of the vertebral column. The lead which gives the greatest amplitude of the oscillations varies with each patient and is only obtained by trial. The standard of the string used has also varied, but has generally been at the normal figure of 3 millivolts = 3 centimetres. Lead II has been used simultaneously with one or other of these chest leads, or the two chest leads have been used simultaneously, by employing two strings in the galvanometer. The patients upon whom the work has been carried out were twenty-four in number. They were out-patients, receiving routine treatment with small doses of digitalis or strophanthus, usually XX to XXX minims of the former tincture, or X V to XX minims of the latter tincture, daily.

*The relation of the oscillations to respiration.* As has already been pointed out, one of the main features of the coarse oscillations found in the limb-lead is their phasic character. This feature is also noticed when the method of leading direct from the chest is adopted. It is true that this method, by eliminating a large mass of somatic musculature, must reduce, to a very great extent, the irregularities consequent upon tremor and limb movement, but the contacts, however, are separated from the heart by the lung tissue which, in expanding or contracting, might be responsible for the phasic appearance of the oscillations. This criticism applies both to the chest and limb leads. It becomes of importance, therefore, to decide if the act of respiration has



any effect upon the oscillations. Fig. 1 shows three records, *a*, *b* and *c*, representative of a series taken. In each case respiration has been recorded simultaneously with an electrocardiogram from a chest lead.

The respiratory movements are recorded in the lower curve, inspiration causing an upward, expiration a downward movement of the curve. The electrocardiogram in Fig. 1 (*a*) was taken with the antero-posterior lead, in records *b* and *c*, with the sternal lead. An examination of the curves shows that the appearance and disappearance of the oscillations is in no way related to respiration. During the inspiratory phase of record *a* the oscillations may (*w*) or may not be present (*x*); while in one expiration (*y*) there may be none, and in another expiration (*z*) they may be obvious. This lack of relation is also clearly shown in Fig. 1, records *b* and *c*, by comparing the phases *w* with *x*, and *y* with *z*.

Moreover, if a series of curves is taken, and the presence or absence of oscillations is noted for the respective acts of inspiration and expiration, the following figures are obtained :—

Act.	Number of acts counted.	Oscillations.	
		Present.	Absent.
Inspiration .. ..	90	66	24
Expiration .. ..	90	61	29

Such figures show that the conclusions arrived at from the records in Fig. 1 are sound, and that there is no respiratory relationship.

A further fact is brought out by the curves; the amplitude of the oscillations is not affected by respiration. A comparison of the same portions of the curves displays this clearly. A table compiled in a similar manner to the foregoing shows the following :—

Act.	Number of acts counted.	Oscillations.	
		Waxing.	Waning.
Inspiration .. ..	15	7	8
Expiration .. ..	15	8	7

It appears evident, therefore, that respiration has no effect upon the amplitude or the presence or absence of oscillations, obtained from direct leads. The phasic appearance of the oscillation is not dependent upon or associated with respiration.

*Comparison of curves from lead II, with those of chest lead, taken simultaneously.*

Having ascertained that the phasic character of the coarse oscillation is not due to respiration, we may pursue the matter further. If a phasic activity of the auricle as a whole is the causative factor, leads taken direct from the chest should give similar records to limb leads, and in simultaneous curves of chest and limb leads the phases should correspond. That the curves obtained from chest leads have phasic characteristics is evident from Fig. 1. In Figs. 2, 3, 4 and 5, a series of records is shown in which curves from lead II and the chest are recorded simultaneously. In each case the upper curve is from lead II and the lower from the chest lead. Fig. 2 shows a condition not frequently encountered; it will be seen that throughout the curve of lead II a series of slow and coarse oscillations can be traced. The form and amplitude of the oscillations changes constantly throughout. In the lower curve, the sternal lead, similar slow oscillations can also be traced throughout; these show less change in amplitude and form. Moreover, if the slow oscillations of the lower curve are compared with the upper it is found that they are coincident in time. In the curve from lead II, at the periods (a) and (b), a finer and more rapid oscillation occurs while the chest leads still records the slow oscillation.

Figs. 3, 4 and 5 are more representative. In Fig. 3 the coarse oscillations in the curve from lead II are only definite over restricted portions of the curve, the remainder being free from them. The coarse oscillations, however, in the chest curve are to be traced continuously throughout, though they show some irregularity in form and amplitude. When the slow oscillations are present in both curves they are coincident. In the curve from lead II, Fig. 4, there are ill-defined and rather rapid oscillations, and an occasional larger irregularity. The chest lead records conspicuous slow oscillations throughout with the exception of the short period a. These oscillations are irregular in form and amplitude. Careful examination of the curves shows that the larger irregularities in lead II are coincident with those of the chest lead.

Fig. 5 is a more extreme example. Lead II exhibits small and rapid oscillations throughout, and also a number of coarse oscillations. In the chest lead slow oscillations varying in form and amplitude are continuously present. Harmony between the slow oscillations in the two curves can usually be traced, but the finer and more rapid oscillations in lead II have no counterpart in the chest lead. Such curves, which are representative of a large number taken, bring out clearly two important facts. The first is that the periods of the curves of limb leads from which the coarse oscillations vanish find no simultaneous counterpart in the curves of chest leads. Correspondence of the phases of coarse and fine oscillation cannot be established in simultaneous curves from limb and chest leads. From this it is evident that the phases which are relatively smooth or present fine

oscillations in the curves of limb leads do not represent a decline or fundamental change in the auricular activity.

The second point clearly shown is that an estimation of the rate of the general auricular movement, based upon the oscillations in lead *II*, is precarious. In the first place the curve, as has been shown above, is not necessarily a full picture of auricular activity, and, in the second place, it is complicated by oscillations derived from the large mass of somatic musculature included between the contacts. With regard to leads *I* and *III* these same objections hold. They are exaggerated in lead *I*, in which slow oscillations are infrequently seen, or when seen are often conspicuously distorted by fine oscillations from the muscles of the arms.

#### *Simultaneous records of two chest leads.*

It has been seen, in the previous sections, that curves of limb leads are not fully representative of auricular movement, and that they are complicated by oscillations derived from other sources than the auricles. The chest leads are more truly representative, largely eliminating somatic oscillations as they do. But that does not constitute the whole difference, for coarse oscillations are more continuously present in the chest leads than in the limb leads. It is presumed that the difference is due to the more favourable planes in which the former are taken. Even in direct leads, however, as has already been pointed out, the coarse oscillations die away from time to time; and we have, therefore, instituted a further enquiry with the idea of ascertaining if the quiescent phases of these curves in reality represent a fundamental change in the character of the auricular action, or if, on the other hand, the disappearance of oscillation in the chest lead is a feature of the lead rather than of auricular activity.

For this purpose four copper discs were used and simultaneous curves from the sternal and the antero-posterior leads taken.

Figs. 6, 7, 8 and 9 are examples of such curves. If either of the curves in Fig. 6 is examined separately it is obvious that there are periods during which the slow oscillations become ill-defined or split into finer oscillations; for instance *b*, in the top, and *a*, *c*, *d* and *e*, in the bottom curve. If, however, the two curves are taken in conjunction, the slow coarse oscillations can be traced throughout the record, for, when they become split or ill defined in one curve they can be easily picked up in the other. The only possible point at which exception might be taken to this statement is the stretch marked *e* in the figure, where the top record is confused by the proximity of the two ventricular complexes. Where the slow oscillations are prominent in both curves, although there is evident correspondence, they are not always absolutely coincident in point of time.\*

\* This lack of absolute coincidence is under separate enquiry.

Fig. 7 is a further example : a comparison of the two curves again shows that if the two curves are taken in conjunction the slow oscillation can be traced throughout, though there may be short periods in both curves during which they are ill-defined or absent ; at one period *a*, they are ill-defined in both curves. The slow oscillations of the two leads again correspond. In Fig. 8 the coarse oscillation is to be traced practically throughout the top curve ; where there is doubt the lower curve fills the hiatus. Rapid oscillation or disappearance of oscillations in one curve coincident with slow oscillation in the other is well displayed. The slow oscillations correspond in the two curves, before and after the disturbances. In Fig. 9 there is an unusually regular slow oscillation in the lower curve, where it continues without break, and requires no support from the upper curve. On the other hand, the continuity of the slow oscillations is frequently broken in the upper curve, and replaced by more rapid oscillations. Such curves show that a single chest lead, though more representative of auricular activity than the limb leads, does not always indicate the whole of the auricular events, as the appearance of rapid oscillations, or the complete failure of the coarse oscillations to record in one lead, coincident with their appearance in the other, clearly shows. Our records as a whole convince us that a slow underlying movement is always continuous in fibrillation ; but to demonstrate this continuity it is necessary to employ at least two relatively favourable leads recording simultaneously. The auricular mechanism is such that the plane for favourable leads is frequently changing. This is shown by the waxing of oscillations in one lead, while they wane in another. From time to time two such chest leads as we employ may become unfavourable, and consequently coarse oscillation may momentarily disappear from both.

We conclude that the phasic character of the oscillations in the chest leads and in the limb leads is a feature of the lead used in recording the auricular movement rather than of the auricular activity.

*Rate of the oscillations.* As a single chest lead curve is open to the objection that it may not fully represent the auricular movement it becomes important to decide which type of oscillations represents the underlying movement of the auricle. With regard to the more rapid oscillations of the chest lead, it can be seen that these oscillations in reality represent slow movement, but that the electrical representations of this movement are split or notched owing to the lead recording them becoming unfavourable, thus giving the impression of a more rapid movement. This is well seen in Fig. 9, at periods *a* and *b*. It is concluded that the slow oscillations are not favourably represented, because when the rapid oscillation appears in the upper curve it carries with it the skeleton of the slow oscillation which is continuous in the lower curve, and both before and after the disturbance occurs, harmonious slow oscillations in the two curves are found. This is again shown in Fig. 6, *b*, and 7, *c*. In all cases the slow main oscillations can be identified in one lead during periods when, owing to notching or splitting, the other gives an impression of greater frequency. There are

many examples of the minor degrees of notching, insufficient to disguise the main oscillation, throughout the figures. It is reasonable to assume that when, over the same period, slow oscillations occur in one lead coincident with rapid oscillations in the other, that the slow oscillation represents the general movement. It is well known that the movement of a single excitation wave through the muscle of the heart will give rise to a number of deflections, or in the case of the auricle to a main oscillation which is notched: but it is difficult to imagine that two or more independent excitation waves should give rise to a combined oscillation continuing to maintain relative constancy of form for long periods. The slow oscillations of considerable amplitude which typify the curve of chest leads must, so it seems to us, represent a single basal movement, and from them the rate of movement is most safely to be calculated. It is to be noted, nevertheless, that the slow oscillation varies slightly but continually in rate; consequently, in short stretches of curve, varying rates are calculated. Moreover, the periods during which the oscillations are clearly defined are short, so that, except when the oscillations show unusual regularity of form, or when the ventricular activity is slow, the rate has to be calculated for a short series.

In the table appended the rates are calculated from series of 10 or more well-defined oscillations of considerable amplitude, notched or otherwise greatly distorted waves having been avoided. The table shows that the oscillations have a rate of about 470 per minute, and that the variation in rates as it is calculated from short stretches of curve is about 90 oscillations per minute. Exceptional cases are met with in which the variation is greater, when it may amount to as much as 200 per minute. The highest rate met with lay a little over 600 per minute, and the lowest at 300 per minute. It is shown by the curves, and by the figures of the table, that in any one patient the rate is constantly changing within certain limits. These changes in rate are due to variations in the lengths of the oscillation cycles and to grouping of shorter or longer cycles from time to time.

*Form of the oscillation.* It is difficult to point to particular oscillations as types, as they are constantly changing in amplitude, shape and duration. But in all curves they conform in type in greater or less degree. When the lead is favourable, and the oscillations are large, they consist usually of a sharp upstroke followed by a more gentle downstroke. Usually, in fact, they closely resemble the oscillations found in auricular flutter. The resemblance in curves from limb leads has been referred to frequently by other writers, notably by Robinson,<sup>5</sup> and Hewlett and Wilson.<sup>1</sup> It strongly suggests that the origin is similar in both conditions. The amplitude of the oscillations varies greatly in some curves, and but little in others. There appears to be no special period of the heart's cycle which is associated with large or small amplitude. Systole or diastole of the ventricle appears to be without effect (see Figs. 7 and 9).

*Rate of oscillation.*

Patient No.	Number of short series counted.	Average rate.	Highest rate (one series of ten)	Lowest rate (one series of ten).
1	12	467	500	435
2	12	418	500	300
3	15	446	480	420
4	11	510	600	430
5	6	429	473	360
6	12	426	500	390
7	16	500	540	430
8	4	461	480	430
9	4	497	510	480
10	19	355	380	300
11	7	425	450	375
12	13	458	520	430
13	10	585	620	500
14	5	494	540	420
15	9	452	480	420
16	8	588	600	530
17	8	489	550	450
18	6	431	470	400
19	7	455	540	420
20	6	416	480	420
21	13	440	470	400
22	13	464	550	420
23	2	430	430	430
24	4	390	450	340
Average ..	9.2	473	504	414

*Reversal in direction and form of the oscillation.* In Fig. 10 a record of two simultaneous electrocardiograms from chest leads in a clinical case of auricular fibrillation is shown.\* The cycles have been measured in the lower curve, and written vertically above each cycle. The oscillations *a* to *h* may be described as beginning with a sharp upward phase from which

\* It happens that at the date this record was taken digitalis or strophanthus therapy had not been commenced in this case.

the curve descends, at first abruptly and then more gradually: the same events are then repeated. They are almost regularly placed and have similar amplitudes. The length of these cycles varies from 0.143 to 0.159 of a second. They are followed by a series of oscillations, *j* to *m*, which appear to be reversed in direction and form: each may be described as beginning in a downward phase, at first gradual, but ending more abruptly: the curve then rises abruptly and the events are repeated. These oscillations are also regularly placed, and vary little in length, being about 0.160 of a second. The apparent reversal of form and direction is associated with a change in the level at which the oscillations lie: though the position of the zero line is not ascertainable, it is clear that the first oscillations lie mainly above, and the last oscillations mainly below it. The cycle *i*, in which the change occurs, is shortened by the apparent prematurity of the movement *j* which follows it. The same change is suggested again by the form of the last half of the same curve. A comparison of the two groups shows that the oscillations are of approximately the same length and amplitude, but have similar but reversed characteristics, and it is concluded that the general flow of the excitation wave, relative to the sternal lead, became reversed. A similar change in direction and form is suggested in phases of the lower curve, Fig. 5. Such change in the form of the oscillations as is here described is a very unusual event. It has been seen in the curves of two patients only.\*

*Favourable and unfavourable leads.* The observations which have been described in this paper convince us of the importance of the position of the lead, in attempting to obtain a true representation of auricular movement in clinical cases of auricular fibrillation. In lead *II*, as has been clearly shown in the curves, the distortions, notchings and disappearance of the oscillations are much commoner than in either of the chest leads. The lead, apart from its other imperfections, is considered to be in a less favourable plane for registering auricular movement than either of the chest leads described. This is borne out by the fact that when contacts are arranged on the chest in the line of lead *II* the results are not favourable: and it is found that, in general, any position which does not approximate to the two general positions described gives a less favourable result. The two positions described gave the most constant records of coarse oscillations, though, as has been pointed out, the auricular activity may change from time to time, and one or other of these leads may for the moment become unfavourable and record the oscillations imperfectly. The idea of favourable and unfavourable leads is emphasised because it is sufficient to explain all the features of the oscillations met with in the curves of chest leads on the assumption that the auricle is maintaining a fairly regular and continuous movement, but that the general direction of the excitation wave relative to the contacts changes from time to time and in greater or lesser degree.

\* The other case was under digitalis treatment.



Such a conclusion is fully supported by the curves obtained. Of the two direct chest leads the antero-posterior lead is on the whole the more favourable. The position of the most favourable leads is usually in or near to the sagittal plane of the body.

### *Discussion.*

It has been shown in this article that single electrocardiograms from clinical fibrillation of the auricles are insufficiently representative of the general movement of the auricle. When simultaneous leads are used, and when these two leads are suitably arranged upon the chest wall, it becomes clear that the groups of rapid oscillations, such as are often to be seen in a single lead, are in reality complex representations of a single movement, and the small amplitude and subdivision of the resultant curve is due to the lead being unfavourable for that particular movement. There is very distinct evidence that in all cases of fibrillation there is a main movement of excitation waves at about 470 per minute and that the movement is continuous. It also seems evident that, speaking quite broadly, this movement is a movement which is repeated. The general and usual repetition of oscillations of a type from moment to moment is hardly to be explained in any other manner. But that there is change is shown because the repetition is rarely accurate and because from time to time the oscillations disappear temporarily from a given lead. The disappearance of oscillations from one curve is not to be explained by a discontinuation of the main movement but by a more decided alteration in direction: the very occasional examples in which an apparent reversal in direction and form of the oscillation is seen in a single lead conforms to this conclusion.

Now the general form of the oscillations in the curve bears a striking resemblance to that seen in cases of auricular flutter, which in a previous article of this series<sup>1</sup> has been regarded as a simple circus movement: it has also been pointed out in a previous article<sup>3</sup> that in impure flutter the auricular complexes of the electrocardiogram become distorted and somewhat irregular in their incidence. These changes have been ascribed to a change in the path taken by the central circulating wave and by its centrifugal offshoots. If the simple circus movement is responsible for the auricular complexes of flutter, then it is difficult to avoid the conclusion that the oscillations of fibrillation have a similar origin. The present observations seem compatible with the idea that clinical fibrillation is a state of flutter, in which, as the experimental work goes to show, the wave follows a sinuous and changing path. The rate of movement in clinical flutter is about 300 per minute, in fibrillation it is about 470 per minute. There is approximately the same increase in the rate of movement as is to be seen in passing from the usual rate of pure flutter to that of very impure flutter in the dog. The conclusion at which we arrive, namely, that the oscillations seen in clinical curves are produced by a single though varying circus movement, is based



upon the observations in the present article, taken in conjunction with the simultaneous observations upon animals recorded in the preceding articles of the series, and in the article which immediately follows.

### CONCLUSIONS.

1. In clinical fibrillation, limb leads give curves which are not fully representative of the auricular movement, partly because oscillations are introduced from the muscle of the body and partly because the planes in which the leads lie are unfavourable.

2. By adopting favourable chest leads, and especially by using simultaneous chest leads, the coarse oscillations can be shown to be continuously present at a rate of about 470 per minute.

3. The most favourable plane for chest leads is usually near the sagittal plane of the body.

4. In fibrillation the form of the oscillation, in general, closely resembles the auricular waves in electrocardiograms of auricular flutter.

5. The phases of coarse oscillation found in curves obtained from cases of clinical fibrillation, both with limb and chest leads, is not dependent upon nor associated with respiration.

6. (a) The clinical curves are explained if it is assumed that in fibrillation the excitation wave is single and moves through a re-entrant path which varies from cycle to cycle. (b) The phasic appearance and disappearance, the distortion, and the notching of the oscillations in chest leads are ascribed to a change in the direction which the circulating waves take relative to the contacts in travelling.

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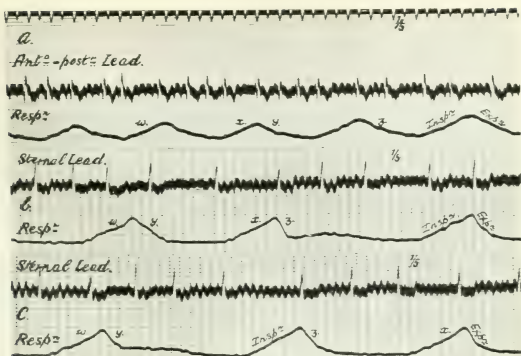


FIG. 1. Case No. 3, respiration and chest lead electrocardiogram recorded simultaneously.

(a) Case No. 3. Electrocardiogram, antero-posterior chest lead, top curve; standard 3 mv. = 1 cm. Respiration, bottom curve; inspiration "up," expiration "down." Time, one-fifth of a second.

(c) Case No. 21. Electrocardiogram, sternal chest lead, top curves; standard 3 mv. = 1 cm. Respiration, bottom curve; inspiration "up," expiration "down." Time, one-fifth of a second.

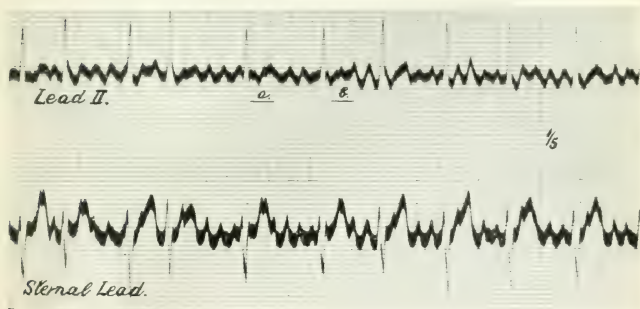


Fig. 2. Case No. 3. Limb lead (lead II) and chest lead electrocardiograms recorded simultaneously. Lead II; top curve, standard 3 mv. = 3 cm. Sternal lead: bottom curve, standard 3 mv. = 2 cm. Time, one-fifth of a second.



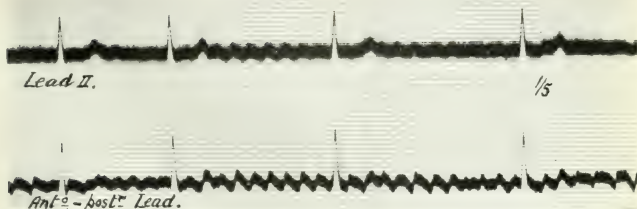


Fig. 3. Case No. 14. Limb lead (lead II) and chest lead electrocardiograms recorded simultaneously. Lead II top curve. Anteroposterior lead: bottom curve, standard limb-stance. 3 mv. = 3 cm. Time, one-fifth of a second.



Fig. 4. Case No. 7. Limb lead (lead II) and chest lead electrocardiograms recorded simultaneously. Lead II top curve, standard 3 mv. = 3 cm. Anteroposterior lead: bottom curve, standard 3 mv. = 4 cm. Time, one-fifth of a second.



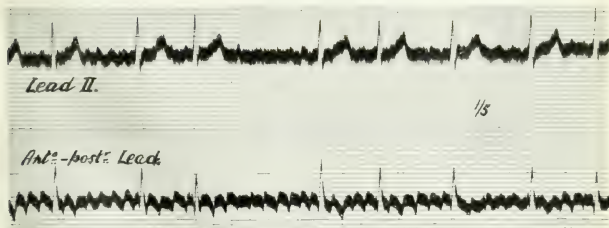


Fig. 5. Case No. 4. Limb lead (lead II) and chest lead electrocardiograms recorded simultaneously. Lead II, top curve. Antero-posterior lead: bottom curve, standard (both strings) 3 mv. = 3 cm. Time, one-fifth of a second.

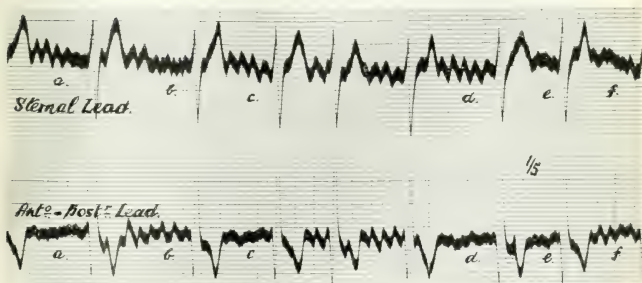


Fig. 6. Case No. 6. Two chest lead electrocardiograms recorded simultaneously. Sternal lead: top curve. Antero-posterior lead: bottom curve, standard (both strings) 3 mv. = 3 cm. Time, one-fifth of a second.





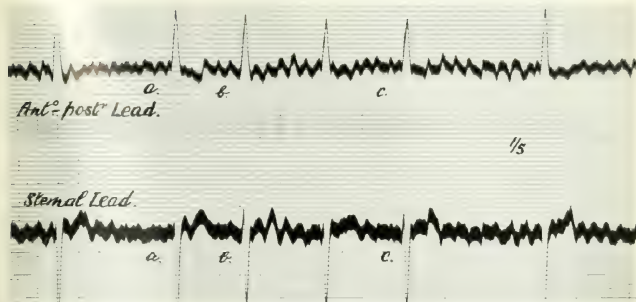


Fig. 7. Case No. 4. Two chest lead electrocardiograms recorded simultaneously. Antero-posterior lead: top curve. Sternal lead: bottom curve, standard (both strings) 3 mv. 1 cm. Time, one fifth of a second.

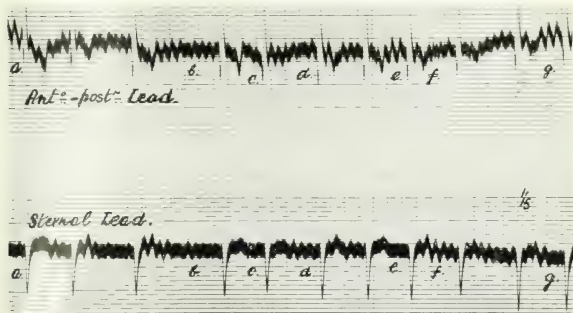


Fig. 8. Case No. 13. Two chest lead electrocardiograms recorded simultaneously. Antero-posterior lead: top curve. Sternal lead, bottom curve, standard (both strings) 3 mv. 1 cm. Time, one fifth of a second.



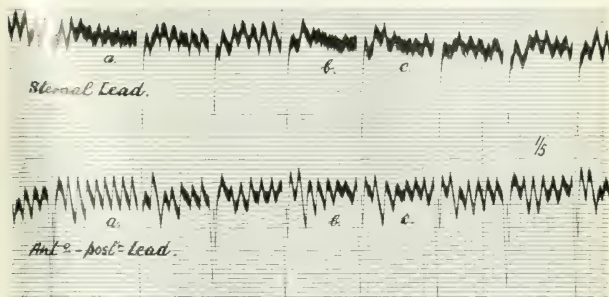


Fig. 9. Case No. 6. Two chest leads electrocardiograms recorded simultaneously. Sternal lead, top curve. Antero-posterior lead, bottom curve, standard (both strings) 3 mv. = 3 cm. Time, one-fifth of a second.

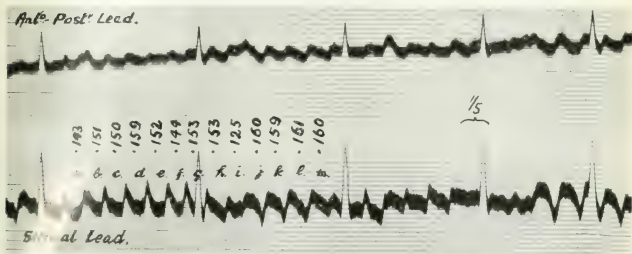


Fig. 10. Case No. 11. Two chest lead electrocardiograms recorded simultaneously. Antero-posterior lead, top curve. Sternal lead, bottom curve, standard (both strings) 3 mv. = 3 cm. Time, one-tenth of a second.



## OBSERVATIONS UPON FLUTTER AND FIBRILLATION.

### PART IX.—THE NATURE OF AURICULAR FIBRILLATION AS IT OCCURS IN PATIENTS.

By THOMAS LEWIS.\*

#### *An observation upon impure flutter.*

BEFORE proceeding to the main subject of the present article an observation is to be described which confirms a conclusion of a previous article. The term impure flutter has been used to designate varieties of flutter, disturbed in lesser or greater degree. It is the smooth course of the excitation wave which is disturbed, and the interference appears on occasion to be very local. This conclusion rests chiefly upon observations in which simple irregularities in the direct leads are compensated: the auricular complexes in limb leads presenting throughout no sign of disturbance. In support of the same conclusion, a record (Vol.VII, page 335, Fig. 10) has been published, showing that at one point of the auricular surface a series of excitation waves appeared regularly, while the simultaneous limb-lead indicated disturbed flow in some other region of the auricle. The conclusion that a disturbance in the smooth flow of the excitation wave in flutter may be purely a local event is one of consequence to the hypothesis which would explain fibrillation: the record now to be described supports this conclusion.

The record is shown in Fig. 5. It is one of the simplest of a series taken from the same animal,† all of which showed either impure flutter or fibrillation of the auricle. The curves were taken simultaneously from three sets of closely paired contacts, placed in line upon the body of the auricle and parallel with the sulcus terminalis. The arrangement of the contacts, each pair of which covered 8 millimetres of muscle, is shown to the right of Fig. 1, in which the deflections of the record are charted. The method of charting is similar to that which has been used previously.‡

\* Working on behalf of the Medical Research Council.

† All the dogs used for the observations of this article were fully anaesthetised with morphia, paraldehyde and ether throughout the experiments.

‡ As the amplitude of the deflections varies little, these are drawn of equal height in the diagram to simplify it.

Consider the last five charted deflections *j* to *n*. The events are regular. In each record is a series of deflections which, by their downward direction, all indicate that the excitation waves to which they correspond strike the *c* contacts first of all; the order of precedence in the three curves is harmonious with the direction of the deflections, each excitation wave strikes contacts 1, 2 and 3 in that order. The waves are proceeding regularly from the inferior caval to the superior caval region. But at the two points the record is disturbed, namely, by waves *c* to *j*. In the centre curve (*i* in Fig. 5) an upright deflection appears, and it is slightly but definitely premature (0.1289 of a second): during the preceding cycle a different form of disturbance is seen in lead 3, here the deflection is slightly but definitely delayed (0.1412 of a second) though its form does not alter. Both these disturbances are *precisely compensated*; compensation occurs at once in the case of the premature beat: in the case of the delayed beat, compensation is hindered because the excitation wave *i* is premature in lead 3 in sympathy with its prematurity in lead 2. The precise compensation of the double disturbance is appreciated when the time relations of deflections *f* and *g* are compared with those of deflections *j* and *k*, and when it is noticed that in lead 1 the deflections are regular in their incidence over the disturbed period. Now the two disturbances, prematurity of one deflection and delay of the other, do not appear to be connected; for in an earlier part of the record, similar disturbances are seen (waves *a* and *c*), but here they are separated by deflections (*b*) having the usual time relations to each other.

The excitation waves which strike the first pair of contacts are waves emanating from the central circus movement at regular intervals. Usually the same excitation waves, or corresponding and parallel waves, flow regularly over the second and third pair of contacts, yielding a regular and repeated motion. But the waves *c* and *j* take a slightly quicker path to the second pair of contacts; these waves have deviated from their accustomed course; to the waves *a* and *h* there has been some slight obstruction in their passage to the third pair of contacts. The courses of the waves are indicated in a diagrammatic fashion in the figure. The irregularity of flow is a local affair; the contacts have been so placed that all have not been affected. The disturbance occurs in one case between the first and second pairs, in the other case between the second and third pairs.

#### *Definition and preliminary discussion of auricular fibrillation.*

In previous articles of this series the word fibrillation has been used in speaking of a form of disordered auricular action. Now the term "auricular fibrillation" does not as yet convey a precise or universal meaning; it has been defined, deliberately or by inference, in different ways by different workers. It has been defined upon the basis of visible or mechanically recorded events in the auricles, of its influence upon the ventricle, of the hieroglyphic of the electrocardiogram. The term has usually been extended

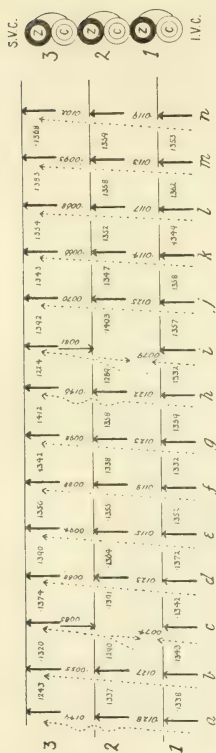


Fig. 1. *Dog LD.* (Record 8.) A portion of Fig. 5 is charted. A diagram of the contacts, as they were arranged on the tricus terminalis is shown to the right of the chart. The heavy arrows represent the time relations of the intrinsic deflections of the record to each other; the arrows are drawn up or down to the corresponding base lines according as the deflections were upwardly or downwardly directed in the curve. The direction of the arrow indicates the direction in which the excitation wave passed the corresponding pair of contacts. The cycle lengths are written horizontally and the transmission intervals vertically in decimals of a second. The broken arrows represent the course of the excitation waves over the contacts as a whole.

to include the disturbance which we have renamed the state of *rapid re-excitation*. As it is used by successive writers, the term shifts its scope, the definition alters as our knowledge of disordered auricular action grows. While such change in terminology forms a natural sequence to new observations, it is at the same time undesirable, tending as it does to confuse discussion. Much as a fixed definition is needed, it may not be possible at the present stage to offer one which will enjoy universal acceptance. In searching for such, two considerations stand out prominently: the definition should be in the nearest possible accord with the general idea of the term's meaning as it is now current, and it should be chosen with forethought for its stability. These two considerations are not necessarily compatible: a definition's stability usually hangs upon its precision and closeness, and the general idea may prove neither precise nor close. In such circumstances one of two courses is open, a definition may be chosen for its precision and narrowness and with a view to effecting change in the current idea of the object defined: or, on the other hand, it is chosen to maintain this idea, temporarily at all events, while some risk of instability is accepted. The choice will largely depend upon the extent to which the current idea is deemed of consequence. In searching for a definition of the term auricular fibrillation, while engaged in the present observations, these considerations have decided in favour of the second course, since the current idea of the term's meaning in this instance appears to be of paramount importance. "Auricular fibrillation" is a term now used most frequently to denominate the clinical state, and a close definition, based on experiment, might in the future find itself in conflict with the clinical meaning: were that to become the case, the result would be unfortunate. Although the term was originally used to describe a condition witnessed in experiment, yet this consideration should not be allowed to weigh heavily: it is more than counterbalanced by the importance of maintaining the present clinical sense of the term. The last is now based ultimately on electrocardiographic records, the term "auricular fibrillation," as it is used clinically, *implies that more or less conspicuous and continuous oscillations of varying form and dimensions, and of auricular origin, are to be discerned in leads from the limbs*. A chief difficulty in attempting more strictly to define the term at present arises out of the apparently complete transition between states which I have so far called "impure flutter" and disorders of somewhat higher grade.

This method of defining fibrillation on the basis of clinical records has the advantage of bringing us at once to our critical problem, which is to enquire into the nature of those disorders of the human heart which display the electrocardiographic curves at present generally associated with the term "auricular fibrillation."

In attempting to analyse what is happening in the auricle while that chamber is fibrillating, in the sense of the foregoing definition, it would be unsound to consider any after-effects of stimulation, which are not proved to yield electrocardiograms (curves from the limbs) of the clinical type.



For this reason those after-effects are chosen which are of sufficient length. During the progress of long-continued after-effects we may record curves simultaneously from two direct leads and, from time to time, may transfer the lead from one pair of contacts on the auricle to contacts on the limbs. Thereby we sample the electrocardiogram from time to time during the continuation of the after-effect, make it reasonably certain that the mechanism is comparable to the clinical disorder, and also assure ourselves that the mechanism is in the general sense unchanging. An even better plan is to record with three strings, maintaining one of them in connection with the limbs, and using the remainder to record directly from the auricle: this plan has been adopted in later experiments by using a single and a double string galvanometer simultaneously.\* There are other and even more serious objections to the analysis of curves obtained from short after effects: short after-effects, produced by stimulating the auricle, lack the stability of clinical fibrillation, which is one of its most striking features: they are constituted for the most part by responses of the auricle to a local state of rapid re-excitation, a state so far unknown to clinical pathology. The local state of rapid re-excitation may last some 10 or 15 seconds: it is unsafe to accept any curve therefore as an example of fibrillation, which is inscribed before the after-effect has been in progress for 20 seconds or preferably longer; those after effects which last many minutes, an hour or longer, are evidently the most valuable for our analysis. These necessary precautions make the observations much more tedious, for, in most animals, short after-effects alone are to be obtained: it is only by repeated experiment and by seizing the opportunities as these present themselves, that sufficient material is to be obtained.

In an earlier article it has been shown that the continued after-effects of auricular stimulation are of varying degrees of complexity. From pure flutter we pass to simple examples of impure flutter, and from these to more complex examples in which eventually the basal or circus movement shows manifest signs of disturbance. Repeated evidence has been obtained that the impurity of flutter is produced by hindrances to the natural progress of the excitation waves, whereby they are deflected and their courses become sinuous and inconstant. The view which has been adopted is that in clinical fibrillation this sinuosity of course is universal and affects not only the centrifugal paths but also the central path, along which the basal and re-entrant wave passes. A first enquiry which suggests itself, is the degree to which this process is carried in fibrillation of the auricle, and especially the degree in which the basal circus movement becomes disturbed. That fibrillation, once established, continues long after its initiating cause is withdrawn, in itself argues powerfully for its dependence upon re-entry of the excitation wave. When we consider that impure flutter, itself maintained by a central circus movement, passes imperceptibly into the

\* The instruments being set up in parallel and recording on the same plate.

disorder of higher grade, and that these disorders are characterised in electrocardiograms by oscillations which bear often a striking resemblance to those of impure flutter, it is already difficult to escape the conclusion that fibrillation is likewise controlled by circus movement. What has not yet been discussed sufficiently is whether the circus movement is single or multiple. Briefly, we have to ascertain if the movements of the auricle at any moment are governed by one or more circulating waves. In the examples of impure flutter, which have been described, it is clear that there is but a single re-entrant wave; it is equally clear that the course of this wave is disturbed: it is not so accurately repeated as it is in instances of pure flutter. Will an increased variation in the central path sufficiently account for the phenomena of fibrillation; or must we suppose that several circuit movements exist?

This and associated problems will now be considered.

#### OBSERVATIONS UPON EXPERIMENTAL FIBRILLATION.

In attempting to analyse impure flutter, a stage is reached at which, owing on the one hand to the altering form of the auricular complexes, and on the other to the sinuous courses of the centrifugal waves, anything like a complete analysis of the paths taken by the waves becomes impossible. The standard of measurement in comparing the time relations of successive cycles is lost when the auricular complexes become broken or irregularly divided; the intrinsic deflections cannot be taken as true indices of the circus movement owing to their variable delay in transit. Nevertheless, analysis is possible to a point. In single curves and in series of curves from the same after-effect, it is the rule to find that most of the deflections are of similar direction and of similar form. This similarity is independent of the muscle region from which the curves are taken. The general direction indicated by the curves of a series is harmonious, indicating that at different parts of the surface the general direction is similarly governed. Thus, the general direction may be up\* the tania, up the body of auricle along a parallel course, and from base to tip of the right appendix. In all cases the general direction seems to be up the *S.V.C.* and down the *I.V.C.*, i.e., in a direction contrary to the blood stream. It should be understood that these directions are by no means universally followed by individual waves; they are the directions which predominate. These observations are compatible with the view that the waves are controlled by a circular movement (clockwise or anti-clockwise as the case may be) which, though varying, repeats the same general rotation.

Such being the conclusion, we should expect to see a considerable degree of harmony between curves taken from closely adjoining muscle areas and to find, in the intervals separating corresponding deflections of the two curves,

\* Or down, as the case may be.

evidence of the direction of flow compatible with that derived from the direction of the deflections.

Figs. 6 and 7 were taken from an auricle during a period of fibrillation lasting 11 minutes; Fig. 6 was taken  $3\frac{1}{4}$  minutes, and Fig. 7, 5 minutes after the end of the provocative stimulation. Three pairs of contacts had been placed on the body of the right auricle parallel to the tænia terminalis, and about  $1\frac{1}{2}$  centimetres from it; in the first record, the two lower pairs (2 and 3) were used as direct leads and the top string of the record was used to record simultaneously from lead *II*. In the second record the top string, hitherto recording from lead *II*, was connected to the top pair of auricular contacts (1), and simultaneous curves from three direct leads were recorded. The lead from each of the three pairs of contacts was so arranged that the Z contact lay towards the superior vena cava: an excitation wave passing from above downwards over all contacts would thus yield an upright deflection of each string. The distance between any two Z contacts was 8 millimetres.

The curve from lead *II* (Fig. 6) presents many points of close resemblance to those of clinical fibrillation. A series of oscillations (*I-II*) is seen in the central portion of the curve; the first and last portions of the curve show oscillations of lesser amplitude and greater rate. The numbered oscillations seem at first sight regular, but measurement of the intervals between them will show that this regularity is not precise as it is in pure flutter, and it will also be seen that the individual oscillations vary in form. Short series of oscillations of this kind are not uncommon in curves classed as clinical fibrillation, and are often responsible for the term "coarse fibrillation," the resemblance of which to flutter has more than once attracted notice. We can with some degree of certainty assume that these eleven oscillations are produced by a single central wave which circulated: for this short stretch of curve is identical with those previously described as complex instances of impure flutter. But the conspicuous oscillations are transient: just as in the clinical curves, the oscillations die away from time to time, to reappear later (see Fig. 11, which is from the same after-effect). Are we to assume that, during the period when the oscillations become less distinct and more numerous, a single circus movement has given place to two or more? The answer is in part found in the curves of the direct lead: these speak for a very similar mechanism throughout. The electrograms both display a number of irregular deflections. In curve 2 (Fig. 6) the passage of each excitation wave is signalled by a movement of the string: sometimes, as in the case of deflection *g*, the movement is of considerable amplitude, but for the most part the amplitude is much less and the passage of the excitation wave is marked by several deflections when the excursion is small. The cause of these small grouped deflections is the passage of the excitation wave in an oblique direction across the contacts. In curve 3 the deflections are better defined; in this curve, as in curve 2, the direction of the conspicuous deflections varies from time to time. In measuring records of this type it is often difficult to fix upon that deflection which most truly represents the passage of the excitation wave, and from time to time errors

of choice certainly occur\*: the rule is to take the beginning of the first steep deflection of notable magnitude at each cycle. The lengths of the cycles are written above curve 2 and below curve 3; the intervals between corresponding intrinsic deflections of the two curves (transmission intervals) are written vertically between them. An examination of these intervals, or coarse measurement, shows that there is obvious and close correspondence between the main deflections of the two curves.† Corresponding deflections of the two curves fall within at the most a few hundredths of a second of each other; as often as not they fall within less than one hundredth of a second of each other. There is evident harmony. At the same time the transmission intervals are dissimilar, they even vary in sign. The majority of the intervals are plus intervals, that is to say, the deflections in lead *II* usually proceed those of lead *III*; the majority of the distinct deflections in both leads are upright; thus it is clear that the general direction of movement is from contacts 2 to contacts 3. This conclusion and the harmonious action of the muscle is even more strikingly displayed by Fig. 7, to obtain which three simultaneous direct leads were used. The deflections of curve 2 in general precede those of curve 3 in Fig. 6; in Fig. 7 the muscle lying beyond contacts 2 has been examined, and in the curve obtained (Fig. 7, *I*) the deflections are seen to precede those of curve 2. Speaking broadly, an orderly movement of the waves from contacts 1 to 2 and from 2 to 3 is displayed. The deflections of these curves are somewhat unusual in the degree of their orderliness; there are but two reversed intervals, namely—0.008 of a second for deflection *e* of curves 1 and 2 and —0.039 of a second for deflection *i* of curves 2 and 3; usually the reversal is more frequent, but it is very rarely so frequent that the general direction of movement remains indeterminate in two simultaneous leads. This record unquestionably shows that the action of the auricular muscle is a harmonious one over a length of 16 millimetres.‡ by which I mean that the same excitation waves pass over the whole of this stretch of muscle. To obtain direct evidence of the distance travelled by the wave is not an easy matter. Consider the uppermost and lowermost curves of Fig. 7; deflections, shown to correspond because they are linked together by the central wave, often fall as much as 0.03 of a second apart,

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\* Such errors are not very material when the curves are treated on broad lines; if such alternative points, as might justifiably be used, were measured in the present record, the conclusions now drawn from it would remain unchanged.

† The exceptions (deflections *h* and *h'* and possibly deflections *p* and *p'*) will be examined at a later stage.

‡ In 1914 I published electrograms<sup>1</sup> from the fibrillating ventricle, which, as I believed, showed little or no harmony between deflections obtained from muscle areas lying very close together. It was this observation, and a mistaken idea that Mines conceived a simple circus movement, which at the time led me to reject Mines' theory of circus movement as the basis of ventricular fibrillation to which it was applied. Observations upon the more simple structure of the auricle have forced me to revise the views of ventricular fibrillation then expressed, and to conclude that the apparent lack of harmony in adjacent leads from the ventricle may be due to the complexity of its muscle layers and perhaps to the more complex nature of fibrillation of the ventricle.

and in this curve the cycles are sometimes no more than 0.10 of a second in length. When curves are taken from muscle areas lying as much as 16 millimetres apart, the transmission intervals are often sufficiently long to bring deflections of one curve into a position nearly or actually midway between two deflections of the other curve. Dealing as we are with cycles which vary in length, and with transmission intervals of varying length and sign, correlation of the deflections in two leads so far apart often becomes unsafe or impossible. This is especially the case when the excitation waves are flowing more in the line of the contacts than was so in the present instance: for in these circumstances the transmission intervals are wider. It is true that on occasion clear and almost invariable correspondence is found when simultaneous leads are taken from areas at a greater distance, but this rarely happens unless the waves which reach the two pairs of contacts diverge to them from a central track of muscle.\* A less direct, though scarcely less decisive, method has to be adopted. Judgment rests upon many records from simultaneous leads over shorter stretches of muscle. If the excitation waves arose from several independent areas, then from time to time discordance between the deflections would be encountered: with the exceptions, presently to be described, such discordance is not discovered. A rule which is not broken is that the great majority of deflections in leads from muscle points 8 millimetres apart are definitely related to each other in point of time. Such evidence shows that in general the whole auricular surface is covered by the same excitation wave or offshoots from it, and that those slight variations which occur from cycle to cycle in the transmission intervals are attributable solely to the sinuous and changing paths which these waves pursue in covering the muscle. Thus, the mechanism of fibrillation seems to be a more simple affair than might be imagined from inspection of the auricle; and the term fibrillation, in its strict sense of independent movement of the fibres, seems scarcely warranted.

*Curves obtained from muscle boundaries.*

There are certain parts of the auricle to which the excitation waves of the normal heart beat travel and come to an end, because they find no further channel open to them. Thus, the normal excitation wave comes to an end in the normally beating auricle when it reaches the tips of the appendices, and when it reaches the end of the muscle sleeve which is prolonged upwards on the superior cava. The normal excitation wave always travels centrifugally to these muscle boundaries: it pursues a course which is in the line of the appendix, or which is approximately at right angles to the free edge of muscle on the superior cava. Curves suggesting reversed courses are never obtained in these situations when the heart is beating

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\* For example, when curves are taken from the superior cava and right appendix, and the waves move to both these points from the region of the tenia.

naturally. The tip of the right appendix and the muscle lying outside the pericardial reflection on the superior cava are particularly suitable for the further investigation of sinuous movement: for if sinuous movement were a universal phenomenon in fibrillation, it would be anticipated that curves taken in these situations might display conclusive evidence of it. It has been stated that the course of the waves in general is up the appendix from its base to its tip, and up the superior cava against the direction of the blood stream. But the sinuous movement of the waves produces striking exceptions to the rule when individual waves are considered.

A record taken from an auricle which fibrillated for seven minutes (the records being taken 30 seconds after the onset) is shown in Fig. 8; the top curve is derived from lead *II* and the middle and bottom curves from contacts placed in line with the appendix. The lettered deflections of this figure have been charted in Fig. 2, and the positions of the two pairs of contacts on the appendix is shown in the diagram to the right of the chart. The Z contacts lay towards the actual tip of the appendix. The deflections of the two electrograms form an irregular series in each curve; the cycles vary in length, and the deflections vary in amplitude and direction. For example, deflection *a* in curve 2 is clearly a downward deflection, and deflection *i* and *k* of the same curve are clearly upward. The upward deflections are produced by excitation waves which first strike the Z contact, namely, that lying towards the tip of the appendix: these upward deflections are frequent in lead 2, and from these it is to be concluded that excitation waves often passed down the appendix from its tip towards its base. This conclusion is strengthened by the position of the corresponding deflections in lead 1; these fall generally a little later than the corresponding deflections of lead 2 (see deflections *d*, *i* and *k*), as would be expected when the excitation waves travel away from the tip of the appendix. Now, if we consider the series of deflections (*a-h*) in the chart, we see in the two leads deflections which correspond, thus conforming to the rule. When an excitation wave is registered by one lead, it is also registered by the other: the intervals between corresponding deflections in the two leads vary in the usual manner, and in a manner sufficiently explained by sinuous movement in the neighbourhood of the contacts. Briefly, each pair of corresponding deflections in the two leads may be ascribed to single excitation waves. Whence are these excitation waves derived? They are derived from the body of the auricle and flow from it into the appendix. Individual waves (such as *d*, *i* and *k*) reach the distal before the proximal contacts; they follow *en route* sinuous though varying paths, such as are depicted in an approximal fashion below the chart. Sometimes the waves pass up the appendix over all contacts: sometimes they pass up and return over the contacts; sometimes in passing up they swerve and meet the contacts at right angles. An alternative to this view is that all the excitation waves arise in the tip of the appendix itself. If this last view is entertained, then a similar sinuosity of course has to be assumed to bring others (such as *a* and *c*) of the same

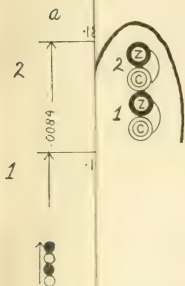


Fig. 2. Dog 1. The excitation wave, directed in a diagram to relative to

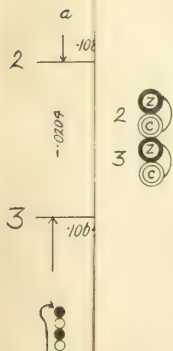
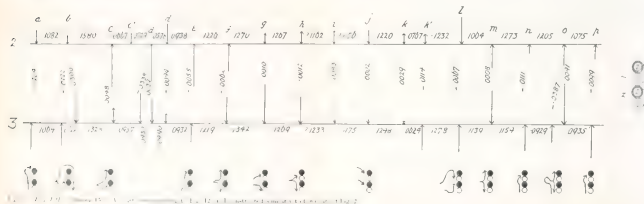
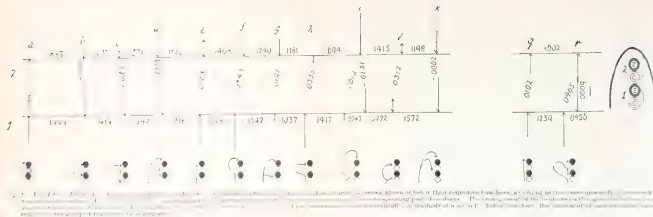


Fig. 3. Dog 3. The excitation wave, directed in a diagram to relative to







series first to the contacts lying nearest to the auricle (contacts of lead *I*) : this assumption would bring us to the same chief conclusion, namely, that waves may pass the contacts before they actually involve the muscle lying beneath them. But this alternative view, and the view that *some* of the excitation waves arise in the tip of the appendix, may be placed out of court because it is the rule that curves of this type are obtained from all the muscle boundaries, such as the tip of the appendix or the sleeve of muscle on the superior cava. Because there is general harmony between the deflections of simultaneous leads wherever these are taken, it cannot be supposed that each of these muscular boundaries always originates distinct excitation waves.

In Fig. 9 are curves from lead *II* and the tip of the right appendix in another animal. Of the appendix contacts, the *Z* contact lay towards the auricle. The deflections of the electrogram are in the main upright, showing that most of the excitation waves struck this contact first. But one deflection *o* is frankly of opposite direction, and in several other cycles (*f*, *g*, *i* and *j*) the deflections are of small amplitude and multiple, indicating that the contacts have been struck, not in their line, but obliquely or at right angles. This electrogram was taken 13 minutes after the end of stimulation, and during a period of fibrillation which lasted just over one hour.

Another record from the same after effect, and taken after it had been in progress for 35 minutes, is shown in Fig. 10. This record consists of two electrograms from the superior cava. As depicted in the diagram drawn upon this record, the two pairs of contacts lay in the line of the cava, a pair (*1*) lying across the pericardial reflection, and the other pair (*2*) lying beyond it and near the edge of the muscular sleeve. The *Z* contact of each pair lay towards the auricle. The upward deflections predominate over the downward deflections in these curves, and those of the proximal lead (*1*) usually appear first. The general direction of movement is distinctly up the cava, but the waves of excitation do not follow a straight or constant path, they pass up the vessel along sinuous and changing courses : often the proximal contacts are first encountered (notably waves *i*, *j*, *k* and *l*), but from time to time (as in the case of waves *e* and *g*) the most distal contact receives the wave which then travels down the cava : in not a few cycles the two pairs of contacts are struck almost simultaneously (for example, cycles *b* and *c*) and the deflections are of small amplitude and multiple.

During this long period of fibrillation, very many curves were taken from the surface of the auricle : all presented the same features as do those used as illustrations : in simultaneous leads, there was always unison between the deflections, a unison disturbed only in such degree as might be accounted for by irregular movement of single waves from point to point. A sinuous movement of the wave seems universal in fibrillation, and extends to the most distant parts of the auricle.

*Examples of seemingly discordant action.*

If the curves taken by means of direct leads are judged broadly, it may be said that they present evidence of a co-ordinate action of the muscle; co-ordinate in the sense that the surface of the muscle is involved by successive excitation waves which spread over it. When we examine the curves in greater detail, we detect examples in which the method of excitation at first seems to be more complex. In considering simultaneous leads, and attempting to identify corresponding deflections in each, such correlation cannot always be effected. In a majority of curves, which include 15 or 20 cycles, one or more exceptions of this kind is usually to be found. A certain number of these discordances are more apparent than real. Thus, when the excitation waves strike the contacts laterally, the curves tend to become confused by the multiplicity of small deflections: though this is rarely sufficient to interfere with broad analysis (see Fig. 10, curve 2), it may and does interfere with accurate measurement. In other curves, deflections are introduced from time to time by the ventricle, but these are as a rule sufficiently small to be negligible. Fig. 8 is an example in which they are distinct; the deflections marked *v* should be compared in their incidence with the ventricular complexes of lead *II*. Some deflections still remain to be explained; these are of two kinds and are described under the succeeding sub-headings.

*Twin deflections.* In analysing curves taken directly from the auricle, it is necessary to identify those deflections which correspond to the passage of excitation waves beneath the contacts. When these are measured, the analysis can proceed. The deflections are recognised because their amplitudes are usually greater than those of other deflections in the curves, and because of their steepness. From time to time, in curves taken from auricles beating at high rates, deflections of this class are paired in the curve in a peculiar manner. The interval which separates the two deflections of the pair is often notably short and may have a value of but 2, 3 or 4 hundredths of a second, usually it is somewhat longer; a second notable and almost constant feature is that the two deflections are of opposite direction. Paired deflections of the kind considered are illustrated in Fig. 4, *A* and *B*. In Fig. 4, *A*, the first deflection (*d*) is directed downwards and is followed after 0.0379 of a second by an upstroke (*u*) of equal amplitude. Fig. 4, *B*, is similar, but the upstroke now precedes the downstroke (the interval being 0.0479 of a second). Such paired deflections are derived from auricles in which the absolute refractory period is estimated at about 0.08 of 0.10 of a second or more; the refractory period is that of an auricle beating at a high rate, but otherwise uninfluenced. In these circumstances it is difficult to imagine that the two sharp deflections represent two excitation waves, each of which has traversed the same muscle fibres: the interval between the two waves is often much too short, yet it is impossible to avoid concluding that each deflection

represents an excitation wave flowing very near to or actually beneath the contacts. The two deflections are produced by two excitation waves coming from opposite directions, and traversing the same sheet of muscle tissue, but not precisely the same strand of fibres: probably in many cases the one excitation wave passes immediately beneath the contacts, while the other courses through parallel muscle lying a little distance away.

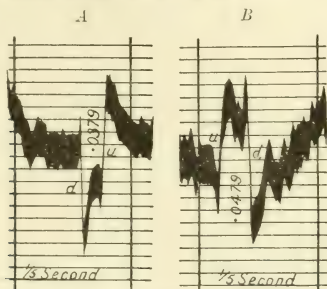


FIG. 4. *Doig (LS. (Record 25.)* Twin deflections in electrograms from a fibrillating auricle.

In previous articles these paired deflections have been described on several occasions. Thus in Vol. VII, page 255, a record (Fig. 6 of that paper) is described which was taken from an auricle responding to a high rate of rhythmic stimulation. In that instance it was shown that both deflections were derived from a single excitation wave originally: the view taken was that the propagated excitation wave travelled near to the contacts without actually involving the muscle beneath them, that it turned sharply and came back through the muscle on which the contacts were lying. The interpretation of these paired deflections may or may not have been correct in its detail: but the first conclusion, that both waves were derived from the same mother wave, is scarcely questionable. Another example of a similar phenomenon is to be seen in Fig. 9 of the same paper. In this case rhythmic excitation waves were propagated from the dorsal surface of the superior cava towards contacts on the ventral surface. Some of these rhythmic waves reached the contacts by travelling in one wall of the cava, others by travelling in the opposite wall, the corresponding intrinsic deflections being upwardly or downwardly directed. The curve considered shows a relatively abrupt transition from one form to the other. At the actual transition, however, stands a composite deflection ( ) in the figure) in which an upwardly directed deflection is followed after a brief interval by a downward deflection (marked \* in the figure). The upward deflection is placed in series with the

preceding and similar deflections: the downward deflection in series with similar deflections which succeed it. In this instance there can be little doubt that the propagated excitation wave, spreading from the dorsal surface of the cava, has coursed through right and left wall simultaneously, and that its two crests have met in the neighbourhood of the contacts. The third example described is that charted in Vol. VII, page 319, and described at page 315. It is from an example of impure flutter: the curves show a short series of paired deflections, a series which is repeated with considerable accuracy from time to time; the picture is a striking one, and the arrangement of the deflections is such as to show again that the two deflections of any pair are twins of the same mother wave. It would appear from these examples, and from the circumstances in which they were obtained, that a pair of deflections may be produced by a single excitation wave, which turns sharply and attempts a re-entrant course, or by a wave which branches and proceeds in the form of two crests, these eventually curving like horns and coming from opposite directions to meet in the neighbourhood of the recording contacts. Paired deflections so produced may be conveniently referred to as twin deflections. They are seen in curves from auricular muscle which is beating so rapidly that the waves are propagated slowly from point to point and in general pursue sinuous paths; and they are seen in these circumstances only.\*

It must be evident, however, that while without exception the examples of paired deflections so far cited have been examples of twin deflections, paired deflections of a similar kind might be produced by the conflict of excitation waves distinct at their origin. Paired deflections of the kind described are frequent in the curves from the fibrillating auricle, and it might be held that the individual deflections are not true twin waves; but the conclusion at which we arrive from the study of impure flutter curves is the more satisfactory. The auricle is beating at the rates at which twin deflections are expected in the curves. The paired deflections occur singly or in groups, their arrangement and the circumstances in which they are seen usually suggest or show their common origin. Thus, the last deflections of Fig. 8,  $r$  and  $r'$  in curve 1, are of this kind (see Fig. 2, end of chart). These two deflections correspond to a single deflection in curve 1. Now the deflections of these two simultaneous curves have been considered already at some length, and it has been concluded that the excitation waves were passing from the base to the top of the appendix; some found their way directly over the contacts; others passed up to the tip and encountered the contacts for the first time on the return journey. If, in passing sinuously up the appendix, a path is taken near to but not actually through the muscle upon which the contacts rest, it might be expected that some impression would be left upon the proximal contacts, and that the nearer the upward path lay to the contacts the more distinct the impression would be. To explain the

\* More direct investigation of twin waves does not seem possible; local and temporary barriers cannot be produced where and when the experimenter wishes.

deflections  $r$  and  $r'$  of the curves, it may be supposed that the excitation wave, in passing up the appendix and near to the proximal contacts ( $I$ ), produced the first deflection  $r$  of the corresponding curve. The two remaining deflections fall about 0.046 of a second later, and almost, if not quite, simultaneously: to explain them, it has to be supposed that the wave curves and enters between the two pairs, and spreads upwards and downwards over them. A somewhat similar example of twin deflections is to be seen in an earlier part of the same record ( $i$  and  $i'$ ), though the course of the wave is different and the twin waves are separated by the unusually large interval of 0.0743 of a second. Here it is supposed that the excitation wave swerved towards the proximal contacts in its upward course for an instant, producing the small deflection  $i$  in curve 1: that it proceeded to the tip of the appendix and returned through the muscle on which the contacts lay and in their line, producing the deflection  $i'$  of curve 2 and  $i'$  of curve 1. The unusual separation of  $i$  and  $i'$  in lead 1 is to be accounted for by the length of this circuitous path.

It is notable that the two instances of paired deflections occur in the curve from the proximal lead, and not in that of the curve taken from contacts nearest the muscle boundary. This illustrates the rule: for while paired deflections of the kind considered are common enough when the lead is from the centre of a muscle sheet, they are very rare in curves taken from its edge. The reason for this is obvious if we hold that the paired deflections arise from a single wave: for, in these circumstances, the chance that a wave, which is approaching a boundary, will return, diminishes as it approaches this boundary: on the other hand, if we hold that separate waves arise in the body of the auricle and also in the tip of the appendix, we should expect to see paired deflections in the curves of both leads with equal frequency.

Examples of paired deflections, similar to those now described are to be seen in Fig. 6 (deflections  $b$  and  $b'$ ,  $p$  and  $p'$ ). Fig. 11 is another record from the same after-effect and from similar leads. It shows a whole series of paired deflections  $a$ ,  $b'$ , etc.. There is clear correspondence between deflections  $a$ - $g$  in the two curves: the transmission intervals are uniform: but whether the deflections  $b'$ ,  $c'$  of curve 3 correspond to the deflections which come before or after them in curve 2 is not at first evident: the deflections  $b'$ ,  $c'$ , etc., gradually approach the deflections which succeed them as they are traced from left to right.\* The arrangement is such that it is this series ( $b'$  to  $g'$ ) which eventually becomes established (in deflections  $i$ ,  $j$ ,  $k$ , etc.). When established, the deflections  $j$ ,  $k$ , etc., bear to each other in the two curves the same time relation as do the deflections  $a$ ,  $b$ , etc., of the curves in its opening phase. Thus, the three sets of deflections,  $a$ ,  $b$ , in curve 1 and  $a$ ,  $b$ , and  $b'$ ,  $c'$ , in lead 2, are linked together: this suggests their common origin.†

\* The intervals in curve 3 are  $b'-b = 0.0754$ ;  $c'-c = 0.0645$ ;  $d'-d = 0.0466$ ;  $e'-e = 0.0532$ ;  $f'-f = 0.0461$ ;  $h'-h = 0.0319$  of a second.

† This series of paired deflections in lead 2 has many striking points of resemblance to those previously described in Vol. VII, page 319, Figs. 3 and 4: in that instance their time relations to the central movement strongly favoured a common origin.

The appearance of twin deflections is very local: they are almost always confined to one lead, as in this instance (see also Figs. 6 and 8). This is so, even though the two pairs of contacts lie no more than 8 millimetres apart. If the individual deflections of each pair were derived from separate sources, if the odd and even series were controlled by separate circulating waves, the phenomenon of pairing would be seen only when the contacts were so fortunately placed that the waves from the two sources met between them. That a pair of deflections may be due to the meeting of two waves is not questioned: what is questioned is that these two waves come from independent sources. Pairing is too frequent in the curves of fibrillating auricles to admit this explanation. If waves emanated from two or three sources, the lines of conflict would be relatively few and paired deflections would not be recorded frequently. If the meeting is explained as the meeting of separate crests of the same excitation wave moving along parallel but sinuous paths, then evidence of such conflict should be frequent in the curves. It is of course open to us to suppose that these paired deflections sometimes represent the collision of separate crests of single waves emanating from one of several co-existing circulating waves. To accept this view is to accept a complex explanation, when a simple one suffices. Further, the hypothesis of several independent though conflicting circus movements is opposed by other observations. Of these some have already been discussed. Perhaps the most convincing argument against the presence of several circus movements is the frequent appearance of well formed oscillations in the curves of lead *II*, waves which in form, in incidence and in rate are too reminiscent of the waves of flutter to permit us to entertain much doubt that they are similarly derived. This brings me to remark upon a feature of the present record (Fig. 11). During the phase in which the twin waves appear, the oscillations of lead *II* are smaller and very rapid. In the later stages they are larger and more regularly placed: here it is not difficult to trace the skeleton of the series of oscillations (*I* to 22).\* It might be argued from this record that during its later stages a single circus movement controlled the auricle, but that in the first phase a second movement of the same kind interfered, and that the paired deflections and the more rapid oscillations of lead *II* might thus be explained. The association is accidental, as a comparison with Fig. 6 suggests: actually the coarse waves start a little before the paired deflections end in Fig. 11. The decrease in size and increase in rate of the oscillations of lead *II* is ascribed to another cause, which will be considered at a later stage.

A last example of paired deflections is shown in Fig. 12: the record is published to emphasise the frequency of pairing, and to display a form of curve derived from lead *II* which, while differing from those previously described in the more broken character of its oscillations, unmistakably resembles many curves of clinical fibrillation. It was taken from the same

\* Measurement will show that these oscillations are not quite regular in incidence, neither are they regular in form.



animal, as was Figs. 6 and 11, but at a later stage of the experiment.\* The record exhibits the action of the auricle half a minute before the end of an after-effect of five minutes' duration. This curve is charted and interpreted in Fig. 3. The interpretation of the paired deflections ( $b$ ,  $b'$  and  $o$ ,  $o'$ ) is very similar to that adopted for those already considered. Broadly speaking, the electrograms of this record are like those previously described: there is general unison between the deflections in the two leads, accompanied by the usual variation in the transmission intervals. The record shows at one point what may be interpreted as paired deflections in the two leads: the deflection  $k$  of lead 1 is represented by a small notch in lead 2, the deflection  $k'$  of lead 2 is represented by a small upward jerk in lead 1. A relation of this kind is comparatively rare in the curves of the fibrillating auricle. Necessarily the interpretation of such events is problematic.

*Waves lost in travelling.* That deflections may be added to curves from time to time is seen from the study and interpretation of twin deflections. In other curves deflections are missing.

In analysing the curves of impure flutter in a previous article it was pointed out and emphasised that the deflections in direct leads are frequently of slower rate than are the auricular complexes in lead *II*, which represent the central movement. That is so, because the centrifugal waves travel slowly and with difficulty and, as their course is long, their passage is not always completed. Reference may be made to Figs. 1 and 2, Vol. VII, page 317, in which this view is sufficiently illustrated.

In auricular fibrillation, to identify the main auricular oscillations is not always easy, but where they are distinct, a similar state of affairs is very apparent. Thus, in these portions of Figs. 6 and 11, in which well-defined oscillations appear in the electrocardiograms, the rate is approximately 580 to 590 per minute: the rate of the deflections in the electrograms over the same periods is about 480 to 500. Owing to the irregularity of the deflections in the direct leads and the impossibility of identifying the main oscillations in lead *II*, except over short stretches of curve, it is impossible accurately to correlate one and the other or to show which centrifugal waves fail; but that they do fail is made evident by comparing the local and general rate of beating with the same rates in the curves of frankly impure flutter. Given that waves sometimes fail to travel the full course in fibrillation, we should expect to find direct evidence of this from time to time. The deflection  $o$  in curve 1 (Fig. 7) a deflection which finds no representative in the companion curves, probably illustrates such failure. Occurring in lead 1 it is the more noteworthy, for the contacts of lead 1, as the transmission intervals show, lay nearest to the source of the waves. Blocked waves of this kind constitute a relatively infrequent, though readily understood, exception to the rule that the activation of different muscle areas is in detail harmonious.

\* The leads were the same as in Fig. 6.

To sum up, the excitation waves in fibrillation spread as co-ordinate waves, though they travel along paths which are often very sinuous. Curves from simultaneous direct leads show deflections which in general correspond; the exceptions to this rule are of two kinds. On the one hand, a single excitation wave appears to yield from time to time not one but two deflections (twin deflections) in such a curve; on the other hand, waves are occasionally propagated as far as one pair of contacts, but not as far as another. Both these phenomena are fully explained by hindrance, partial or complete, to the passage of excitation waves travelling in partially refractory muscle. The first phenomenon may be accounted for by supposing that occasional waves strike, and are deflected to the side of, muscle refractory at the time, and that they return and sweep through these barriers as these a little later become responsive; they are also to be explained by supposing that waves split on such barriers and that the two crests meet beyond. The second phenomenon is explained by supposing that a wave flows into so extensive a region of refractory tissue that further progress in any direction is for the instant impossible. The curves of the direct leads, treated broadly and compared with those of impure flutter previously described, speak for a single central wave circulating continuously. Although the curves become from time to time very complex, and the deflections are so arranged as possibly to suggest that they are derived from more than one source and interfere with each other, yet a closer examination renders this interpretation less tenable. The complexities of the curves are compatible with a single source of origin, and are to be explained on the ground of sinuous movement.

*Remarks on the oscillation of lead I I.*

The analysis of impure flutter was carried in a preceding article to the point where it became evident that the central wave was breaking up, as evidenced by irregularities in the incidence of the auricular complexes and by their growing distortion. The curves of fibrillation take us a step further. The oscillations displayed by this mechanism, when they are distinct and of considerable amplitude, are similar to those of disturbed flutter; but often these oscillations are transient, they die away or disappear abruptly, to be replaced by fine oscillations of smaller amplitude. Is there a fundamental change of mechanism when the form changes? The reply is given by the direct leads, which show no simultaneous change in general form or arrangement. Accepting the view that there is no fundamental change, it becomes obligatory to explain the altered form of oscillation in the limb lead. Light is thrown upon this question by such records as that of Fig. 13. This record is from a period of fibrillation in which the ventricles were responding at a very slow rate and in which the auricular elements of the curve are consequently well displayed. The curve from the direct auricular lead is of the usual type; the oscillations of lead I I are very irregular. In this curve the outlines of the first few oscillations are distinct (*a*, *b*, *c* and *d*). As the curve proceeds they become less distinct, though the skeleton of almost



rhythmic waves may be traced up to the oscillation marked *j*. These main oscillations occur at a slightly faster rate than do the deflections of the direct lead. The curve in its opening phase is similar to one of frankly impure flutter, in which the auricular complexes are grossly distorted and irregular. The distortion is due to the sinuous and changing paths taken by the waves as a whole: the irregularity in incidence is due to the varying path followed by the central wave.

To count the auricular complexes in flutter, even when these are naturally bifid, is not difficult, for the same form is repeated: but to count complexes which are irregularly bifid, which are from time to time split into more components and which are irregular in incidence, is soon beyond our power. The rate of oscillations, counting all in the curve, is in fibrillation no criterion of the rate at which the auricular muscle is beating. The rate of the main oscillations in limb leads is similar, maybe it is sometimes a little faster, than those seen in examples of impure flutter previously recorded.

When the form of the main oscillations changes, as it does in Figs. 6 and 11, and oscillations of faster rate and lesser amplitude appear, there is no need to conjure up new and interfering circus movements or faster circuit movements. Such changes are sufficiently explained by a single circus movement following, in phases or irregularly, somewhat different paths. As the path changes, so the plane in which it moves alters and the limb-lead becomes favourable or unfavourable, as the case may be, to the full display of the general movement in the auricle. The conclusions of this paragraph are not based exclusively upon direct exploration of the auricle, which speaks for a single and in general co-ordinate wave: it is based equally upon the simultaneous studies which Drury has undertaken upon the human heart and which are recorded fully in the article which immediately precedes the present one.

#### *The relation of flutter and fibrillation.*

That clinical fibrillation of the auricles is a state of advanced impure flutter cannot, I think, be disputed: if the observations of this and preceding articles have been correctly interpreted, then both flutter and fibrillation in the auricle have as their underlying basis a single circulating wave: they differ from each other in that in flutter this wave follows a constant anatomical path, while in fibrillation this path varies in greater or lesser degree from cycle to cycle.

Trace the mechanisms up the scale of increasing disorder, and as the scale is ascended the movement is in general faster. The main factor dominating the rate of the movement is the length of the refractory period: the relation to rate suggest that auricles predisposed to fibrillate are those in which the effective refractory period is somewhat shorter, as compared with that of auricles predisposed to flutter. But that apparently is not the sole factor of difference. In auricles predisposed to fibrillate, transmission of the excitation waves from point to point has been shown to become very irregular when it

is delayed (see Vol. VII, page 247), while in auricles predisposed to flutter, transmission, though it may be slow, is similar in rate from cycle to cycle. This difference is to be traced to the size of the refractory barriers which the excitation waves meet in travelling: in flutter they are small, in fibrillation they are larger; in flutter such deviations from the straight path as occur are minute; in fibrillation they are larger and deflect the waves along paths obviously sinuous. The manner in which responsiveness of the tissue is recovered is again the underlying factor, for the barriers, as has been shown, are barriers of refractory tissue.

### *Historical Note.*

Fibrillation was first described in the ventricle by Hoffa and Ludwig<sup>5</sup> in 1850; they produced it by submitting the ventricle to strong constant or faradic currents; a somewhat similar condition in the auricle was described by McWilliam<sup>12</sup> in 1887. Although the term flutter of the auricle was used in McWilliam's paper, auricular flutter was not clearly recognised as a distinct condition until it was described in the human auricle by Hertz and Goodhart<sup>4</sup> in 1908 and by others,<sup>8, 10</sup> in papers which soon followed theirs. Fibrillation of the human auricles was first proved to occur in 1909-10 by Rothberger and Winterberg<sup>18</sup> and the writer<sup>9</sup>; and in the human ventricle by Hoffmann (1911)<sup>6</sup> Robinson (1912)<sup>17</sup> and Halsey (1915).<sup>3</sup> The discovery of these conditions in man has given the chief impetus to the work of the last decade.

In 1884 Kronecker and Schmey<sup>7</sup> believed the co-ordinate beat of the ventricles to be controlled by a nerve centre, the destruction or paralysis of which would produce fibrillation. This view was disposed of three years later by McWilliam, whose paper will always remain a landmark in the history of our knowledge. McWilliam, though agreeing that the ventricular muscle contracts inco-ordinately in fibrillation, argued, on the basis of numerous experiments, that the cause is to be found in the condition of the muscle itself. He laid stress upon its state of excitability, and formulated a hypothesis very similar to that which Mines and Garrey put forward later.

He states (page 308) "Then the excitable (and probably highly rhythmic) muscle contracts, but its excitation instead of assuming the form of a normal beat becomes a peristaltic contraction wave along the complexly arranged and inter-communicating muscular bundles. And if the ventricular muscle is in an excitable state there would naturally occur a rapid series of such inco-ordinated peristaltic contractions. For apart from the possibility of rapid spontaneous discharges of energy by the muscular fibres, there seems to be another probable cause of continued and rapid movement. The peristaltic contraction travelling along such a structure as that of the ventricular wall must reach adjacent muscle bundles at different points of time, and since these bundles are connected with one another by anastomosing branches the contraction would naturally be propagated from one contracting fibre to another over which the contraction wave had already passed. Hence if the fibres are sufficiently excitable and ready to respond to contraction waves reaching them, there would evidently be a more or less rapid series of contractions in each muscular bundle in consequence of the successive contraction waves reaching that bundle from different directions along its fibres of anastomosis with other bundles. Hence the movement would tend to go on until the excitability of the muscular tissue had been lowered, so that it failed to respond with a rapid series of contractions."

In this account the present conception of re-entrant waves is clearly foreshadowed: the conception lacked sufficient support from direct

observation, and consequently failed to carry conviction. There is abundant evidence in the paper to show that McWilliam regarded lowered conduction power as an essential factor, though his account is rendered less clear by his avoidance of the term refractory period.

In 1895 Engelmann<sup>1</sup> suggested that ventricular fibrillation is a condition in which automatic stimuli arise at unusual centres in the ventricle, and that the conflict between waves spreading from these centres is responsible for the disordered action of the muscle. This view, though it has always remained hypothetical, has received much support.<sup>11, 21</sup> It has gained its chief support from observations upon the simple disturbances leading up to fibrillation: emphasis has been repeatedly laid upon the extrasystole as the preliminary disturbance, and fibrillation has come to be regarded by many as extrasystolic in nature. Hypothesis has strayed chiefly because, too generally, extrasystoles, single and multiple, have been regarded as the result of discrete impulses. The close relation between extrasystolic phenomena, flutter and fibrillation is still to be acknowledged; but a newly recognised factor has now to be taken into account. It is that a single excitation wave may pass more than once through the same tissue, that two or more beats may result from a single impulse. We have seen that this possibility was recognised by McWilliam: it has also been recognised as a possibility by Wenckebach<sup>20</sup> and by other writers. The important step taken in recent years has been the proof of its occurrence.

For that demonstration we are primarily indebted to Mayer (1908)<sup>13, 14</sup> who experimented at first with the umbrella of the jelly fish and subsequently with rings of muscle cut from the turtle's heart. This important lead was taken up by Mines (1913),<sup>15, 16</sup> who confirmed and largely extended Mayer's observations.

We are not indebted to Mines for the proof of circus movement, but to Mayer: we are not indebted to him for the first suggestion that fibrillation has circus movement underlying it, but to McWilliam. Our debt to Mines is that his observations into the factors underlying circus movement were thorough and illuminating, that when he re-suggested circus movement as the underlying cause of fibrillation, the suggestion was so reinforced that its most careful consideration became inevitable: it became the more inevitable when Garrey (1914)<sup>2</sup> independently made the same suggestion and showed that in a ring cut from a fibrillating ventricle a single wave continues to circulate. It is to be understood, however, that the work thus briefly described left the ultimate meaning of fibrillation still in the stage of hypothesis. It was at this stage that our own observations began, and it has been our endeavour to carry knowledge from the state of hypothesis to that of conclusion.

In reviewing the history of flutter and of fibrillation it is not possible to omit reference to the important paper of Rothberger and Winterberg (1914)<sup>19</sup>. These workers were the first carefully to examine the fluttering or

fibrillating auricle by means of direct leads. Their observations have especially served to re-emphasise the close inter-relation of flutter and fibrillation: another suggestion, that the length of the refractory period is an important element in determining the kind of after-effect which follows stimulation of the auricle, is notable. This paper of Rothberger and Winterberg's has served further to link up and explain the reaction of the stimulated auricle, when the muscle is under the influence of the vagus or of such drugs as muscarine and physostigmine. It is important to recognise, however, that the term fibrillation was used by these writers to include the state which we have renamed "rapid re-excitation," that this last condition is not equivalent to clinical fibrillation and that their chief conclusions are not applicable to the latter.

It may prove of interest if, while the facts are still fresh in my memory, I now set down the steps which have led my collaborators and myself to accept the theory of flutter and fibrillation as set forth in the present series of articles. From the circumstances of the case, it is largely a personal narrative. In the autumn of 1914 it was decided further to investigate the nature of fibrillation. The war postponed the work until the autumn of 1918. In 1918, although knowing Mines<sup>15, 16</sup> and Garrey's<sup>17</sup> papers, I still leaned to the view that irritable foci in the muscle underlay fibrillation. To this conception I was led by Engelmann's similar hypothesis of fibrillation in the ventricles. At the end of 1914 I published my views in the form of an address<sup>11</sup> and criticised Mines' hypothesis adversely, citing some recent experiments upon the fibrillating ventricle which, it was thought, showed that closely adjacent fibres were excited independently of each other. These observations seemed to me incompatible with the hypothesis which Mines had expressed. In returning to the subject in 1918 it was determined to test the matter in the auricle; believing fibrillation as it affects this chamber to be a more simple condition, it was thought that Mines' view of circus movement applied to it could be the more easily disproved. The methods employed were those which had been developed for exploring the normal beat of auricle and ventricle, namely, the analysis of curves from direct leads. In the first investigations, taken up with Dr. Cotton, short after-effects of faradic stimulation were recorded by means of direct leads, and we searched these curves for evidence of fibre dissociation. We were working for the most part with curves of rapid re-excitation, taken from the muscle near the point of stimulation, and it soon became apparent that far more extensive work than had been intended would be necessary, if even a partial analysis of the curves was to be won; and that it would be necessary to start with relatively simple forms of after-effect and to work up from these. In conjunction with Dr. Foil and Dr. Stroud, the work on flutter was started, and the earlier observations were placed on one side as for the moment unintelligible. We began, fortunately as it transpired, by attempting to follow the path taken by the excitation waves in flutter; it was not until we had repeatedly seen pure and long-continued flutter, that the full significance of experiments on ring preparations was recognised. We were driven slowly to the conclusion that pure flutter consists essentially of a simple circus movement; in coming to that conclusion we were guided, not by McWilliam's or Mines' hypothesis of ventricular fibrillation, but by the dramatic experiments which Mines and others had conducted upon rings of muscle. From the time when we felt able to conclude that pure flutter is comparable to this ring experiment, and that in flutter a wave circulates around a natural opening in the muscle of the auricle, the course of the investigations became simplified: it then became imperative to investigate, first conduction and eventually the refractory period in the mammalian auricle, in which work Dr. Drury and Dr. Bulger joined me; for these two factors were obviously fundamental. From the analysis of flutter, that of simple forms of impure flutter and eventually fibrillation and their reactions to vagal stimulation was a natural outgrowth.

It is to the ring experiments, therefore, that the present series of articles owes its chief inspiration. Our collected papers have brought together a number of observations, hitherto in seeming conflict, and, so it appears to us, have harmonised them. As observations have continued, it has become increasingly clear that a number of independent workers have been making for the same ultimate goal. There comes a time when, with interest in a particular problem widely awakened, the reaching of the goal becomes inevitable: a successful issue does not depend upon the work of this or that group of researchers, it is the natural outcome of progressive work stretching over many years and undertaken by many workers in the same field. As often happens, when work of this kind is brought to an end point, the convergence of many lines of correlated research is for the first time fully displayed, and we see the goal to which they have all been leading us.

## CONCLUSIONS.

Analysis of auricular disorders produced experimentally and yielding electrocardiograms similar to those of clinical fibrillation, shows that clinical fibrillation of the auricle is a condition in which a *single*\* excitation wave circulates continuously through the auricular muscle. The path taken both by the central and centrifugal parts of this wave is sinuous and varies in greater or lesser degree from cycle to cycle. Thus auricular fibrillation, as it occurs clinically, is an advanced variety of impure flutter. The sinuous course of the waves is attributed to barriers of refractory tissue; the chief difference between slightly impure flutter on the one hand and fibrillation on the other is that in the latter the barriers are of greater extent and of more frequent occurrence. In pure flutter the effective refractory period is probably somewhat longer than in impure flutter and fibrillation.

The term auricular fibrillation, though strictly speaking inaccurate, should be retained.

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\* This qualification does not necessarily apply to the fibrillating ventricle.

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In the following records, the standard of the electrocardiograms was 1 centimetre = 1 millivolt, and of electrograms, approximately 1 centimetre = 3 millivolts.

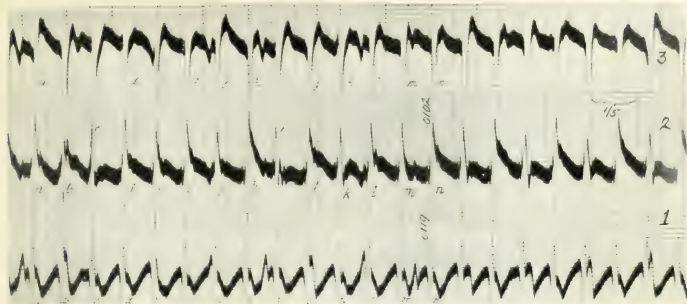


Fig. 5. *Fig. I.D. (Reversal 8)*. Three simultaneous electrograms from the tenna terminals, during a period of auricular flutter lasting a minute. The curves were taken from three pairs of contacts arranged in line on the tenna, the Z contact of each pair being towards the superior cava and 8 millimetres from the next Z contact. The curves are charted in Fig. 1. Excitation waves proceeding up the tenna strike the Z contacts first and yield downward deflections. Time marker in fifths and tenths of a second.

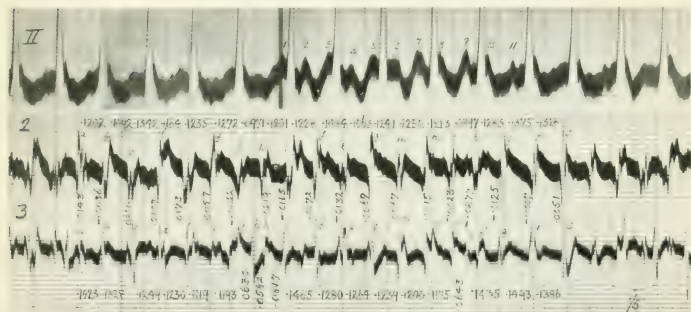


Fig. 6. *Fig. I.H. (Reversal 3)*. An electrocardiogram, lead II, and two electrograms (2 and 3) taken 3 minutes from the beginning of a period of fibrillation lasting 11 minutes. The electrograms were taken from two pairs of contacts laid in line on the body of the right auricle and parallel to the tenna. The contacts of lead 2 lay towards the inferior cava, the Z contact of each pair lay towards the superior cava. The lengths of the cycles are written above and below the corresponding electrograms, the transmission intervals between the electrograms. Time in fifths and tenths of a second.









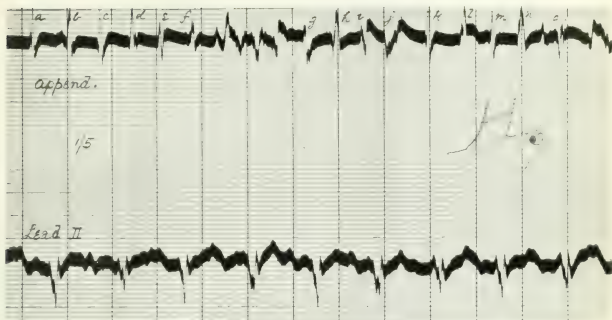


Fig. 9. Dog JS. (Record 23.) An electrocardiogram (Lead II) and an electrogram from the right appendix. Taken from a period of fibrillation which lasted over an hour, and 13 minutes from its onset. The relation of the contacts to the appendix is shown diagrammatically on the record. Time in fifths of a second.

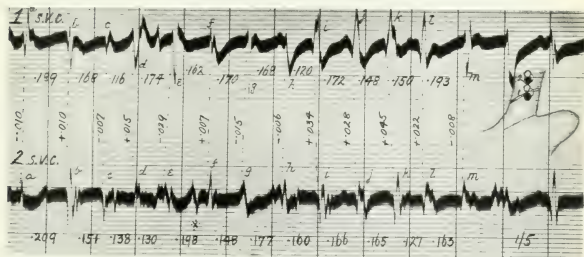


Fig. 10. Dog JS. (Record 30.) Two electrograms taken during the same period of fibrillation and 35 minutes from its onset. As shown diagrammatically on the record, the lower contacts lay across the pericardial reflection on the superior vena, while the upper contacts (1) lay above and in line on the edge of the muscular sleeve. Time in fifths of a second.







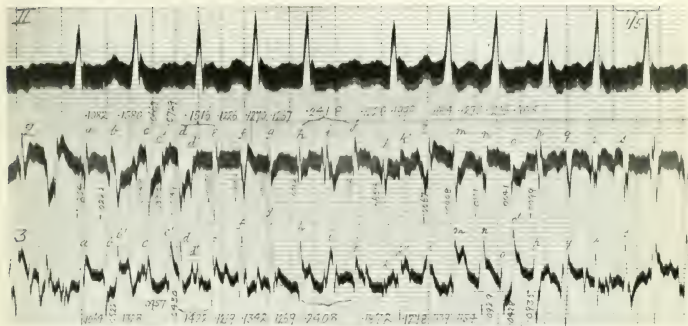


Fig. 12. *Dog L.H. (Record 45.)* Curves taken by the same leads as those of Fig. 11, but towards the end of a separate after-effect of five minutes' duration. The lengths of the cycles are written above and below the corresponding electrograms and the transmission intervals between them. The lettered deflections are charted in Fig. 3. Time in fifths and tenths of a second.

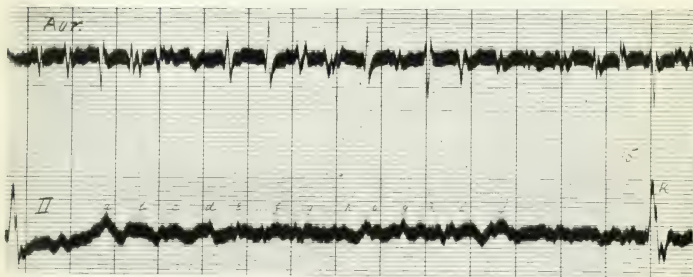


Fig. 13. *Dog YR (Record 20).* An electrogram from the auricle and an electrocardiogram from lead II, during a period of auricular fibrillation. The ventricle is beating slowly. Time in fifths of a second.





# AN EXPERIMENTAL STUDY OF INCOMPLETE BUNDLE BRANCH BLOCK AND OF THE REFRACTORY PERIOD OF THE HEART OF THE DOG.

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It is scarcely more than a decade since the introduction of the string galvanometer made clinical electrocardiography possible, and yet it has become a method of great value and of almost universal interest. One has but to scan the medical journals to realise the rapidity of its growth and the wealth of fact that it has added to cardiology. Until quite recently, however, electrocardiographers have been handicapped by the lack of an adequate analysis of the normal electrocardiogram, more especially of the ventricular complex. Thanks to Lewis and his collaborators, we now have a thorough understanding of the *Q, R, S* group and its relation to the spread of the excitation process in the ventricular muscle. The conclusions arrived at as a result of the experiments reported in the Philosophical Transactions of the Royal Society (3, 5, 6) are so fortified on every side that it is improbable that they will need material revision.

The experiments which we report in this article were devised to test certain conceptions suggested by this work. We cannot review Lewis's papers in detail, and we shall assume that the reader is already familiar with them.

## *Methods.*

The conclusions that may be drawn from any experiment are conditioned by the methods used. We shall describe here, therefore, only the general circumstances of our experiments, leaving each special procedure for discussion in connection with the data furnished by it.

Thirty-two experiments were performed upon dogs, and one upon a monkey of the genus *Cercopithecus*. Large dogs were chosen when they were available. In the great majority of cases morphine sulphate (from  $\frac{1}{2}$  to  $1\frac{1}{2}$  grains according to the size of the dog) was given subcutaneously

about one half hour before the experiment was begun. The animal selected was anaesthetised with ether. The electrocardiographic electrodes were then applied: these were small copper discs about 1 inch in diameter, soldered to binding posts. They were sewn under the skin after the manner described by Lewis<sup>6</sup>: one on the inner surface of each foreleg, where it joined the trunk, and one on the inner surface of the left hindleg. These electrodes were easily and quickly applied, and gave perfect satisfaction; the electrical resistance of the animal and electrodes was usually about 2,000 ohms, and there was never any overshooting of the string or demonstrable polarisation. The trachea was then exposed and a tracheal cannula inserted. The chest was opened along the midline by splitting the sternum, and artificial respiration was begun. A slit was made in the pericardium of just sufficient length to expose the anterior surface of the heart without allowing the organ to slip out of the pericardial sac entirely; in the latter event, it was difficult to maintain the heart in a constant position, and variations in the contact made by it with surrounding structures caused artefacts in the electrocardiogram. In the majority of instances the vagi were divided. This was necessary to avoid sinus arrhythmia, changes in heart rate, and the disturbances of the cardiac mechanism produced by morphine, and to insure a rapid heart rate which was desirable in most of our experiments. A sufficient number of experiments was done, however, without morphine and with the vagi intact to determine that vagotomy had no appreciable influence upon our results. Slight changes in the form of the electrocardiogram took place when the thorax was opened, but these were not of a character to interfere with the experiments. Occasionally minor changes in the form of the electrocardiogram occurred spontaneously; most of these seemed to be due to slight changes in the position of the heart. After exposing the heart, a control electrocardiogram was taken in each lead. From this time onward, the experimental procedure was varied according to the information desired.

All measurements given in this article were made with a Jaquet curve analyser. Great accuracy is not possible with this instrument, but most of the intervals given are correct within 0.003 or 0.004 second. The magnitude of the error is to a great extent dependent upon the sharpness of the points from which the measurements are made.

### *Theory of incomplete bundle branch block.*

We preface the description of our experiments by an account of the course of reasoning which led us to undertake them. We hope in this way to present our work more clearly and in a more natural order.

The course of the excitation wave over the ventricular muscle is known; entering the special conducting system of the ventricles by way of the His-bundle, it passes along the two chief branches of this structure and their subdivisions and spreads through the Purkinje plexus which lines the

endocardial surface of both chambers.<sup>5</sup> From the Purkinje tissue it spreads outward through the ventricular walls toward the epicardial surface of the heart. The speed with which the excitation process travels in the special conducting system is about ten times as great as the speed with which it travels in the ordinary ventricular muscle. The form of the initial deflection (*Q.R.S.*) of the ventricular complex is dependent upon the course pursued by the excitation wave through the ventricular muscle, and the *Q.R.S.* interval is determined by the time taken by the excitation wave to complete its journey.\*

Lesions of the special conducting system of the ventricles may modify the *Q.R.S.* group in two ways: (*a*) by prolonging the time required by the excitation process to reach all parts of the ventricular muscle, and (*b*) by changing the course of the excitation wave, and thus the order in which the various muscle regions pass into the active state. The aberrant electrocardiograms associated with lesions which completely interrupt the passage of the impulse through one of the two chief branches of the His-bundle are well understood. Their peculiar form is the result of the asynchronous activation of the regions supplied by the two branches; the ventricle supplied by the healthy branch passes into the active state in advance of its neighbour, and for this reason shapes the early phases of the initial deflection (*Q.R.S.*). For the long *Q.R.S.* interval of these abnormal complexes there are two possible causes: (1) the delay experienced by the excitation wave in reaching the Purkinje plexus of the ventricle normally supplied by the injured branch, and (2) the increased time taken by the excitation wave to reach all parts of this ventricle because of its abnormal mode of entry, and, consequently, abnormal course. The first cause is surely an important one, for since the conducting systems of the two ventricles are not linked together except through the main stem of the His-bundle, the impulse can reach the ventricle affected by the lesion only by passing through the inter-ventricular septum; and its rate of travel through ordinary muscle is low. The importance of the second cause is less clear. The point at which the impulse enters the Purkinje plexus of the one or the other ventricle will determine to a considerable extent the order in which various areas of the subendocardial muscle of that ventricle are activated; it will determine to a much less extent the time required by the impulse to complete its course through the ventricular muscle supplied by the plexus in question.† It seems probable, therefore, that the long *Q.R.S.* interval of bundle branch block curves is due chiefly to the first cause mentioned.

\* The *Q.R.S.* interval is equal to the time during which the excitation wave is spreading plus the time required by the last muscle region activated to develop its full potential. The time consumed in the latter process is known to be short, and may be assumed to be constant.

† This statement is based on the belief that the Purkinje tissue anastomoses freely; that the rate of travel in the Purkinje plexus is the same for all its parts; and that the ventricular cavities are completely, or almost completely, lined with Purkinje tissue.

Many of the aberrant electrocardiograms obtained from patients are quite unlike the curves seen in experimental bundle branch block. On the basis of the pathological findings observed in cases from which such curves were obtained in life, Oppenheimer and Rothschild<sup>10</sup> have attributed certain abnormalities of the ventricular complex to defective conduction of the impulse in the subdivisions of the branches of the His-bundle and in the Purkinje plexus. One of the chief characteristics of the curves described by them is an abnormally long *Q.R.S.* interval. The experimental evidence bearing on the problem is scanty, but such as there is does not bear out the idea that so-called "arborisation block" produces the type of curve ascribed to it. Furthermore, it is difficult to understand why defective conduction in the smaller branches of the His-bundle should produce more than a very slight increase in the *Q.R.S.* interval. The chief cause of the greatly prolonged *Q.R.S.* interval of bundle branch block curves is here non-operative, for the impulse has free access to the Purkinje plexus of each ventricle. In order to increase the *Q.R.S.* interval, the lesion must, therefore, increase the time required by the impulse to traverse the muscle of the ventricle affected. If one examines accurate drawings of the Purkinje systems of the right and left ventricle, such as those published by Lewis and Rothschild,<sup>5</sup> the difficulty of understanding how any but an extensive lesion can do this will be appreciated. It is not sufficient that the lesion slightly delay the arrival of the impulse at some region that is normally activated early; it must delay the arrival of the impulse at some region that is normally activated late; or it must force the impulse to pursue a path longer\* than the longest normal path. It seems unlikely that a lesion of the freely anastomosing Purkinje tissue can do this unless it is a very extensive one. A lesion of the Purkinje plexus or of the smaller subdivisions of the His-bundle might be expected to have about the same effect upon the activation of the ventricular muscle that the ligation of a freely anastomosing artery has upon the blood-flow in the region which the artery normally supplies. Lesions of those strands of conducting tissue which, in the dog, bridge the ventricular cavities probably have a greater effect upon the duration of the spread of the excitation process than lesions of other parts of the arborisations of the His-bundle branches. It has been shown that section of these free strands of conducting tissue modifies the dog's electrocardiogram,<sup>5</sup> but it has not been shown that it produces a notable increase in the *Q.R.S.* interval. In man the subdivisions of the His-bundle do not, as a rule, bridge the ventricular cavity.

Reflections of this nature made us sceptical of the importance of "arborisation block" in the production of aberrant electrocardiograms

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\* Longer in the sense of more time-consuming.

showing a conspicuous increase in the *Q.R.S.* interval.\* How, then, were aberrant electrocardiograms, not characteristic of bundle branch block as at present understood, but showing an abnormally long *Q.R.S.* interval, to be explained? On considering the possibilities, it appeared to us probable that many of these abnormal curves were due to incomplete bundle branch block.

Lewis<sup>3</sup> has shown that in right bundle branch block the first part of *Q.R.S.* (the first half approximately) is written by the spread of the excitation process in the left ventricular muscle; and that in left bundle branch block the first part of *Q.R.S.* is written by the spread of the excitation process in the right ventricular muscle. He found that if these pure right ventricular effects (dextrocardiogram) and pure left ventricular effects (levocardiogram) were added algebraically in their proper time-relation, a curve identical with the normal *Q.R.S.* resulted. It is clear as a result of this knowledge that the principal effect of a lesion that delays without completely interrupting the passage of the impulse through one of the chief branches of the His bundle will be a shift in the time-relation of right and left ventricular effects, and, therefore, an abnormal combination of the levocardiogram and dextrocardiogram. A less important effect will be a change in the relative mass of septal muscle activated from the right and from the left Purkinje plexus.

Lewis<sup>3</sup> has published careful measurements of both the dextrocardiogram and the levocardiogram of a number of dogs and of one monkey. Using these data, we determined, as a preliminary to our experiments, the effect of shifting the relative positions of these two curves upon the composite curve obtained by their algebraic summation. It was found that when the right ventricular effects were retarded, *R* became shorter and *S* deeper, whereas, when the right ventricular effects were advanced, *R* became taller and *S* tended to disappear. The first curve (*A*) of Fig. 1 shows the effect of advancing the dextrocardiogram 0.005 second; *R* is considerably taller than in curve *B*, which shows the algebraic summation of levocardiogram and dextrocardiogram in their normal time-relation. Curves *C*, *D* and *E* were obtained by advancing the levocardiogram 0.005, 0.010 and 0.015 second respectively. The result is a gradual reduction in the height of *R* and the formation of an *S* deflection. In general, shifting the relative positions of the levocardiogram and the dextrocardiogram produces curves transitional in form between the *Q.R.S.* of the normal complex and the *Q.R.S.* of bundle branch block curves: the composite curve gradually takes on the form of the levocardiogram or dextrocardiogram whichever is made to precede the other.

\* We do not maintain that very extensive lesions of the Purkinje plexus or a toxic depression of the conductivity of the special tissues as a whole cannot increase the *Q.R.S.* interval, but we believe that such disturbances are infrequent. On several occasions we have seen great prolongation of the *Q.R.S.* interval in patients who were moribund. In these instances the increase of the *Q.R.S.* interval was not limited to beats of supraventricular origin; when ventricular extrasystoles occurred, the extrasystolic ventricular complex also had an unusual outline, and showed great broadening of the initial deflections.

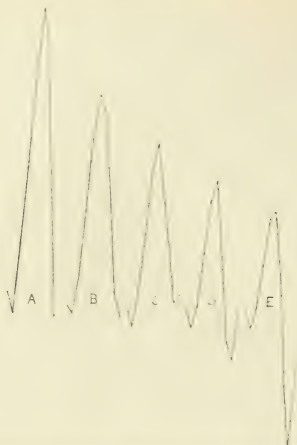


Fig. 1. Curves obtained by the algebraic combination of the levocardiogram and dextrocardiogram in varying time-relations. A.—Dextrocardiogram advanced 0.005 second. B.—Levocardiogram and dextrocardiogram combined in normal time-relation. C.—Levocardiogram advanced 0.005 second. D.—Levocardiogram advanced 0.010 second. E.—Levocardiogram advanced 0.015 second.

*Experimental combinations of the levocardiogram and the dextrocardiogram.*

Having determined the general form of the composite *Q.R.S.* obtained by the algebraic addition of the levocardiogram and the dextrocardiogram in varying time-relations, we attempted to produce abnormal combinations of these two curves experimentally. For this purpose we devised a number of methods which will be considered in order.

*Vagus stimulation in right bundle branch block.* We first tried vagus stimulation in right bundle branch block. When the right vagus nerve of the dog is strongly stimulated, all cardiac activity is for a short time completely inhibited. If the stimulation is continued, the ventricles escape, and in many such instances the form of the ventricular complex indicates that the idio-ventricular pace-maker lies below the bifurcation of the His-bundle. It seems probable that vagus stimulation inhibits all higher centres. It was thought that by cutting the right branch of the bundle we should destroy the influence of the vagi upon all centres below the

cut, and that on vagus stimulation of sufficient intensity an idio-ventricular rhythm of right-sided origin would result. If the supra-ventricular centres were then released gradually we might expect to get interference of two pace-makers and various combinations of the levocardiogram associated with the supra-ventricular pace-maker and the dextrocardiogram associated with the idio-ventricular pace-maker.

We did four experiments of this type. The right branch of the His-bundle was cut according to the method of Lewis.<sup>3</sup> The right vagus was stimulated with a faradic current from a small induction coil. In only one of these experiments did we obtain a transition of the type sought. In some instances it was impossible to produce an idio-ventricular rhythm: in other instances, an idio-ventricular rhythm developed but the ventricular complexes were of the same type as before stimulation. Under the conditions of our experiments, the right vagus did not seem to have a sufficient influence over the lower centres to enable us to obtain a rhythm of right-sided origin. The single transition obtained (Fig. 6) shows complexes of the type expected to result from the abnormal combination of the levocardiogram and the dextrocardiogram. The pure right-sided complexes were not recorded, but the first complex of the curve is shaped in its early phases by right ventricular activity. Each succeeding complex shows an advance of the levocardiogram until in the fourth cycle the fully developed right branch block complex is seen. In the second cycle, right and left ventricular effects occur in nearly the normal time-relation and the result is a complex of relatively normal outline.

*Bilateral bundle branch block.* We next attempted to obtain transitions between a rhythm of right-sided and one of left-sided origin by cutting both branches of the His-bundle. It was first shown by Eppinger and Rothberger<sup>2</sup> that section of both divisions of the bundle does not produce standstill of the ventricles except for a few moments: one of the lower ventricular centres takes on the function of pace-maker. We found that in bilateral bundle branch block the ventricular complex might begin with right ventricular effects, indicating a right-sided pace-maker: it might begin with left ventricular effects, indicating a left-sided pace-maker (Fig. 19): or it might be of relatively normal outline as in the instance described by Eppinger and Rothberger.<sup>2</sup> Providing, as we are led to believe, that only the specialised tissues possess the property of rhythmicity in high degree, the normal type of ventricular complex in bilateral bundle branch block can result only from the simultaneous activity of two pace-makers, one in each branch of the bundle.

We cut both divisions of the His-bundle in five experiments. In one of these, the ventricular complexes were of relatively normal form. In the others, occasional changes in the location of the pace-maker from one side to the other occurred and these shifts were usually accompanied by complexes of transitional form. In Fig. 20, two transitional, or what we may term,



combination complexes, are seen. In the top record, a single complex of normal outline occurs after a long period of ventricular standstill that followed the second cut. In this instance, two centres, one on each side, formed impulses at the same instant. The second combination complex is seen in the bottom strip of record (cycle 2). It accompanies a shift of the pacemaker from the left to the right side, and is the result of the simultaneous discharge of two centres competing for control of the ventricular rhythm.

Transitional complexes did not occur with sufficient frequency in these experiments to make the method of much value for our purpose. The experiments are, however, of considerable interest: they convince us that complete heart block associated with ventricular complexes of varying form is usually due to bilateral bundle branch block and not to a lesion of the main stem of the His-bundle.

*Stimulation of the right ventricle in right bundle branch block.*

The two methods already described were designed to produce abnormal combinations of the normal levocardiogram and the normal dextrocardiogram. In so far as they were successful, they confirmed the idea that such combinations give complexes transitional in form between the normal complex and bundle branch block complexes. The third method employed also gave combinations of the levocardiogram and dextrocardiogram, but in this instance one of these curves was of "extrasystolic" origin.

It has been shown by Lewis<sup>3</sup> and others that, if a systole be produced by stimulation of the surface of the right ventricle, the ventricular complex is of nearly the same form as the ventricular complex of left bundle branch block. The excitation wave initiated at the surface of the right ventricle travels in all directions: its speed of travel in the ordinary muscle is slow, but when it reaches the endocardial surface it spreads with great rapidity throughout the right Purkinje plexus, and its further course through the ventricular walls does not differ materially from that of the excitation wave that enters the Purkinje plexus by way of the right branch of the His bundle. Such differences as exist between the ventricular complexes produced by stimulation of various points on the right ventricular surface and between these and the ventricular complex of left bundle branch block are due to slight differences in the order in which the different regions of the right ventricular muscle are thrown into the active state.

Both the excitation wave which originates at the surface of the right ventricle and that which descends from the auricles in left bundle branch block reach the left Purkinje plexus late. The course of the excitation wave through the left ventricular muscle is probably the same in both cases. In left bundle branch block, the impulse reaches the left Purkinje plexus by piercing the septum. The excitation wave that originates at the surface of the right ventricle has the choice of two routes to the left



Purkinje plexus: it may pierce the septum or it may pass up the right division of the bundle and down the left. From the fact that the form of the ventricular complex produced by stimulating a given point on the ventricular surface before, and that produced after cutting one division of the bundle, are usually almost identical in form (Fig. 15), we conclude that the first route is the one usually chosen, or that the route chosen is immaterial so far as the further course of the impulse is concerned.

The close resemblance of the extrasystolic to the normal dextrocardiogram suggested our third method of obtaining abnormal combinations of right and left ventricular effects. Right bundle branch block was produced by cutting the right branch of the bundle. The surface of the right ventricle was then stimulated with single induction shocks. In our first experiments we used both make and break shocks, and placed them at random. Later, through the kindness of Dr. Joseph Erlanger, we were able to employ a device which supplied break shocks at regular and adjustable intervals. When the rate of stimulation was just a little slower than the heart rate, it was possible to obtain a short record showing the effect of stimulation in each portion of the cardiac cycle. The stimulus used was of sufficient strength to produce a smart painful sensation when applied to the tongue, and to cause, in most instances, a definite notch in the electrocardiographic record.\*

The notch in the record produced by the stimulus is useful as a signal. When the heart responds it is followed by a ventricular complex after a definite† latent period which varies in length with the point stimulated. According to Lewis,<sup>3</sup> the duration of the latent period is determined by the distance of the point stimulated from Purkinje tissue.

Except during the refractory period of the point stimulated, each stimulus applied to the surface of the right ventricle is followed, after a definite‡ interval, by an extrasystolic dextrocardiogram. Each *P* summit is followed after a definite interval, the right branch of the His-bundle being cut across, by a normal levo-cardiogram. By properly placing the stimulus in relation to *P*, and therefore in relation to the levo-cardiogram

\*The presence or absence of this notch in the record is not dependent upon the strength of the stimulus alone, but also upon the distance between the platinum points of the stimulating electrode, and upon the angle made by the line joining the points of the electrode with the line joining the leading off points. When this angle is nearly a right angle, the notch is small or absent: when it is nearly zero, the notch is maximal. Other factors being equal, the greater the distance between the platinum points, the larger is the notch.

†The length of the latent period after stimulation of a given point is constant except for the stimuli which fall just after the refractory period ends. These are followed by a much longer latent period than the stimuli that fall later in the cardiac cycle. It has been shown by Keith Lucas<sup>4</sup> that all stimuli which fall during a short interval immediately succeeding the refractory period are followed by responses at the same delayed moment. Stimuli which fall just outside this interval are also followed by delayed responses. The cause of the long latent period that follows early stimuli is unknown; it may be either a slow development of the local excitation process set up by the stimulus or a slow conduction of the propagated disturbance. The observations of Lucas were made upon striated muscle, nerve and the cardiac muscle of the frog; the galvanometer (capillary electrometer) electrodes were placed directly upon the excitable tissue. We have not made accurate measurements of the latent period in our experiments; but, although indirect leads were used, inspection of the records indicates that in some instances at least the latent period varies in accordance with Lucas's conclusions.

which follows it, a variety of combinations of the levocardiogram and the extrasystolic dextrocardiogram may be obtained. Moreover, since each of these curves follows a recorded event by a definite interval, their time relations can be determined.

To illustrate the method, we may describe experiment 7 in detail. In this instance, we first attempted to cut the left branch of the bundle. Characteristic left bundle branch block complexes appeared immediately (Fig. 7*b*): but a few minutes later the normal type of complex returned (Fig. 7*c*). We then produced right bundle branch block by pressing with the back of the knife-blade upon the right side of the septum: characteristic electrocardiograms developed at once (Fig. 7*d*) and persisted for about one and one-half hours. Complexes of nearly normal outline then returned (Fig. 7*e*). While right branch block was present, the right ventricle was stimulated at irregular intervals by single make and break induction shocks. When the stimulus was applied to the central region, approximately over the point where the right branch of the bundle breaks into its arborisation, the resulting ventricular complex (Fig. 8 complex 4) closely resembled the left branch block complexes (Fig. 7*b*) obtained earlier in the experiment. When the stimulus fell during the *P-R* interval, a combination complex resulted, and in many instances this was identical with the normal complex of the control curve (compare complex 2, Fig. 8, with the ventricular complex of lead *II*, Fig. 7*a*).

In order to show that the *Q.R.S.* of the combination complexes under discussion is a summation of the levocardiogram and dextrocardiogram, we have measured and charted the extrasystolic complex (Fig. 8, complex 4) and the branch block complex (complex 3) of Fig. 8, and have added the ordinates of the resulting curves algebraically (Fig. 2). The time relation in which these curves united to form complex 2, which is charted for comparison with the calculated curve, was determined as follows: *P* precedes complex 3 (the levocardiogram) by 0.088 second and complex 2 (the combination complex) by 0.076 second. The signal of the stimulus precedes complex 2 by 0.02 second and complex 4 (the dextrocardiogram) by 0.02 second. In complex 2, therefore, the dextrocardiogram precedes the levocardiogram by 0.012 second. The curves were charted and added in this relation. In its early phases the calculated curve (Fig. 2*c*) closely resembles the recorded combination complex (*N*). Of course only the first part of *Q.R.S.* of complex 3 (Fig. 8) and the first part of complex 4 were produced by the spread of the excitation wave in a single ventricle; the last part of *Q.R.S.* in each instance is bilateral in origin. Consequently, the calculated and the recorded curves (*C* and *N*) resemble each other in their early phases only. The curve obtained by adding *T* of the extrasystolic complex and *T* of the bundle branch block complex will be discussed in a later section of this article.

Other experimental combinations of the levocardiogram and the dextrocardiogram are shown in Fig. 9. In this instance, the stimulus was



Fig. 2. Lf.—Chart of complex 2 of Fig. 8. Rt.—Chart of complex 4. N.—Chart of complex 2.  
C.—Calculated curve obtained by the algebraic addition of the ordinates of Rt. and Lf.

applied to the conus region and the extrasystolic dextrocardiogram is of greater amplitude than the normal dextrocardiogram. Complex A represents a complete ventricular extrasystole: the signal precedes it by an interval of 0.025 second. The other lettered complexes are combinations of the extrasystolic dextrocardiogram and the normal levocardiogram. The time relation of these curves can be determined in each instance by a comparison of the *S-R* interval (signal to *R*) with the *S-R* interval of complex A, or by a comparison of the *P-R* interval with the natural *P-R* interval of 0.088 second. Measurements of the *S-R* and *P-R* intervals of each lettered complex of Fig. 9 are given in Table I. In the last two columns of the table the interval by which the dextrocardiogram or levocardiogram precedes its fellow is given.

TABLE I.

*The S-R and P-R intervals of the combination complexes of Fig. 9.*

Complex.	S-R Int. Seconds.	P-R Int. Seconds.	Dextro- cardiogram precedes by ; Seconds.	Levo- cardiogram precedes by ; Seconds.
A	0.025	0.026	—	—
B	0.036	0.052	0.036	—
C	0.023	0.057	0.031	—
D	0.022	0.074	0.014	—
E*	0.035	0.086	0.002	—
F*	0.036	0.089	—	0.001
G	0.019	0.090	—	0.006
H	0.014	0.088	—	0.011
I	0.014	0.089	—	0.039
Others	—	0.088	—	—

In complexes *E*, *F* and *G* (Fig. 9) the levocardiogram and dextrocardiogram begin almost at the same time (Table I). These complexes are of relatively normal form; they show, however, the influence of the greater amplitude of the dextrocardiogram. Complexes *B*, *C* and *D*, in which the dextrocardiogram precedes its fellow, are transitional in outline between complex *A* and the normal complex. Complexes *H* and *I*, in which the levocardiogram precedes, are transitional in form between the normal complex and the right branch block complex. All of the lettered complexes are diphasic.

A still better idea of the relation between the relative positions of the levocardiogram and the dextrocardiograms and the form of the combination complex may be obtained from Fig. 10. In this instance, the conus region was stimulated rhythmically at a rate slightly below the heart rate. The result was a beautiful transition from the extrasystolic complex to the right branch block complex. The measurements of Fig. 10 are given in Table II.

\* These complexes follow the signal of a make stimulus. The latent period seems to be longer in this experiment for make than for break stimuli. We are not able to say whether this is usually the case.

TABLE II.

*The S-R, P-R, and Q.R.S. intervals of Fig. 10.*

Complex.	<i>Q.R.S. Int.</i> Seconds.	<i>S-R Int.</i> Seconds.	<i>P-R Int.</i> Seconds.	Dextro- cardiogram precedes by ; Seconds.	Levo- cardiogram precedes by ; Seconds.
1	0.067	0.030	0.043	—	—
2	0.048	0.031	0.064	0.007	—
3	0.043	0.023	0.071	—	0.008
4	0.049	0.010	0.071	—	0.020
5	0.073	—0.014	0.075	—	0.034
6	0.078	—	0.074	—	—

Here again the dextrocardiogram is of greater amplitude than the levocardiogram, and, consequently, it controls the form of the combination complex, not only when it precedes the levocardiogram as in complex 2, but even when it follows it by a short interval as in complex 3. It will be noted that the combination complexes have a *Q.R.S.* interval intermediate between that of the normal complex and that of the extrasystolic and branch block complexes.

A still more gradual transition from an extrasystolic complex to a right branch block complex is shown in Fig. 25. In this instance the progression is not so orderly: complex 5 is transitional in form between complexes 3 and 4. Complex 1 is a complete extrasystole. In complexes 2 to 7 inclusive, the dextrocardiogram precedes the levocardiogram. In complexes 8 to 16 inclusive, the levocardiogram precedes the dextrocardiogram. Complex 17 is a fully developed right branch block complex. The character of the combination complexes is, in general, the same as in the figures previously discussed, but it is desirable to point out the resemblance of complexes 11, 12 and 13 to the type of complex attributed to arborisation block. The measurements of Fig. 25 are given in Table III.

*Summary of the characteristics of the complexes produced experimentally by the combination of levocardiogram and dextrocardiogram in varying time relations.*

The experimental combination of the levocardiogram and dextrocardiogram in varying time relations shows that :—

1. Combination complexes in which the dextrocardiogram precedes the levocardiogram by a considerable interval are transitional in outline between the normal complex and the complex of left bundle branch block.

2. Combination complexes in which the levocardiogram precedes the dextrocardiogram by a considerable interval are transitional in outline between the normal complex and the complex of left bundle branch block.

3. Combination complexes in which the levocardiogram and dextrocardiogram begin at almost the same instant resemble the normal type of complex closely.

4. All combination complexes except those of the third class are diphasic and have a *Q.R.S.* interval intermediate between the natural *Q.R.S.* interval and the *Q.R.S.* interval of bundle branch block.

*Experimental incomplete bundle branch block.*

Having determined the form of complexes produced by abnormal combinations of the dextrocardiogram and levocardiogram, we attempted to produce incomplete bundle branch block experimentally. In our early experiments, we found that attempts to cut one of the bundle divisions frequently produced temporary bundle branch block. Temporary branch block could also be produced by pressure upon the right or left side of the septum. The recovery of the injured branch was usually gradual, and during the stage of recovery we were able to obtain records showing complexes transitional in form between the bundle branch block complex and the normal complex.

The control curves, the transitional curves and the complete branch block curves from such an experiment are shown in Fig. 12 (Exp. 17). In this experiment we attempted to cut the left bundle-division; the characteristic curves of left branch block appeared immediately. The movements of the galvanometer string were watched closely, and when a change in the form of complex was seen to occur, records in the three leads were made as quickly as possible. The central records of Fig. 12 show the type of complex present at this time. These complexes show all the characteristics of experimental combinations of the levocardiogram and dextrocardiogram in which the latter precedes the former; they are diphasic and are transitional in outline between the normal complex and the left branch block complex. Their form and the manner in which they were obtained makes us certain of their origin; they represent the effect of incomplete left branch block upon the form of the dog's electrocardiogram.

A similar series of curves showing the effect of incomplete right branch block upon the form of the electrocardiogram is shown in Fig. 17 (Exp. 21). In this experiment, temporary right branch block was produced accidentally. While stimulating the right central region the electrode was thrust through the wall of the right ventricle; right branch block complexes appeared at once, but did not persist. When it was noted that the injured bundle had begun to recover, records were made at once (central

records of Fig. 17). Later the right branch of the His bundle was cut; the resulting curves (right hand records, Fig. 17) were identical in outline with those that followed the accidental injury of this branch (Fig. 15). The remarks made with reference to Fig. 12 apply to Fig. 17 with equal force, except that here we are dealing with incomplete right branch block instead of incomplete left branch block.

Various stages in the recovery of the right branch in an experiment in which right branch block was produced by pressing upon the right side of the septum are shown in Fig. 22.

From these experiments we may conclude that incomplete bundle branch block produces curves of the form anticipated from a study of abnormal combinations of the levocardiogram and dextrocardiogram.

*Partial bundle branch block.* Lesions of the main stem of the His-bundle may produce: (1) complete A-V dissociation; (2) partial A-V block; or (3) a simple increase in the A-S-V's interval. Lesions of the branches of the His-bundle have so far been shown to produce but two kinds of disturbances: (1) complete bundle branch block, and (2) incomplete bundle branch block corresponding to delayed conduction in the main stem. Do lesions of the bundle-divisions ever produce a disturbance comparable to partial A-V block? We should expect partial bundle branch block to be represented in the electrocardiogram by (a) a gradual increase in the Q.R.S. interval ending with a complex like those of complete branch block followed by a sudden decrease in the Q.R.S. interval; or (b) an alternation in the length of the Q.R.S. interval; the wider complex indicating complete block, and the other impaired bundle branch conduction. That is, we should expect variations in the Q.R.S. interval comparable to the variations of the P-R interval that occur in partial A-V block. We have never seen variations in the Q.R.S. interval of this character either in experimental or in clinical electrocardiograms, and it seems that, if they occur at all, they are of great rarity. That their infrequency is not due to any essential difference between the main stem of the His-bundle and its two divisions is shown by the following observations.

In experiment 22, a cut on the left side of the septum was followed by characteristic complete left branch block (Fig. 18). About 15 minutes later the right branch of the His-bundle was cut. The second cut was followed by a period of ventricular standstill (Fig. 20, top curve) after which the ventricles began to beat independently (Fig. 20, bottom curve). After a short time the left branch, which had not been completely severed, began to recover, and typical partial A-V block ensued (Fig. 21). At this time the ventricular complexes were of the right branch block type. Eventually, the left branch recovered completely, but right branch block persisted (Fig. 18, right-hand curves). It is quite clear, therefore, that, when one branch of the bundle is cut, lesions of the remaining branch have the same effect as lesions of the main stem.



It is obvious that any delay in the passage of the impulse through one of the bundle divisions which amounts to more than three or four hundredths of a second (in the dog) will produce the same result as complete bundle branch block; the impulse will pass around the region of impaired conductivity by way of the contralateral ventricle rather than through it. In most instances of partial *A-V* block, all supraventricular impulses suffer a delay in the main stem of the bundle (or in the *A-V* node) more than sufficient, if it took place in a bundle division, to give the picture of complete branch block. It is true that, in some instances of partial *A-V* block, the *P-R* interval that follows the long ventricular pause is little if any longer than the natural *F-R* interval: but this short *P-R* interval is the expression of an improvement in the conductivity of the region of block that seems to be dependent upon the failure of the blocked impulse to reach the farther side of this region or to produce a ventricular systole. In bundle branch block, the impulse is not prevented from reaching the farther side of the region of impaired conductivity, nor is it prevented from initiating a ventricular systole, and it is possible that under these circumstances no improvement in the conductivity of the region of block occurs as a result of the failure of the impulse to traverse it.\* These considerations, so it seems to us, explain the great rarity or non-occurrence of partial bundle branch block. Incomplete bundle branch block may cause variations in the *Q.R.S.* interval when the heart is beating irregularly. In auricular fibrillation, for instance, it is not improbable that the variations in the period of rest enjoyed by the region of block may cause variations of its conductivity.

*The effect of lesions of the divisions and the subdivisions of the His-bundle upon the form of the ventricular complex.*

In the course of our experiments, we have accumulated considerable data upon the effect of cutting the divisions and subdivisions of the His-bundle upon the form of the electrocardiogram.

So far as the general form of the ventricular complex after section of the chief right or chief left division of the His-bundle is concerned, we can add nothing to the descriptions given by Lewis.<sup>3</sup> We did not obtain, as did he, any right bundle branch block curves in which the chief initial deflection of lead *I* was upwardly directed. We did obtain right branch block curves intermediate in form between this so-called discordant type and the ordinary concordant type in which the chief initial deflection is

\* The improvement in the conductivity of the region of block that follows a blocked beat is difficult to explain. The simple theory of rest and recovery is not adequate. Why does not the attempt of the impulse to pass cause as much fatigue as its actual passage? Why does the impulse that gives rise to an interpolated ventricular extrasystole cause a prolongation of the next *P-R* interval in spite of the fact that it does not traverse the junctional tissues? There are a number of facts that suggest that the improvement in the conductivity of the region of block that follows a blocked impulse is associated with the failure of this impulse to produce a ventricular response.



downwardly directed in all leads. We did one experiment upon a monkey (genus *Cercopithecus*) with the idea of obtaining discordant curves, but we were disappointed; section of the right division produced concordant curves as in the dog. The left division was also cut and complete block resulted.

In all instances in which attempts had been made to cut the branches of the bundle, the heart was carefully examined post-mortem and drawings were made showing the relation of the cuts to the visible conducting tracts. In every experiment in which permanent right or left branch block was obtained, the corresponding bundle-division was found to have been completely divided. We did not study our material histologically, for we felt that further work of this kind was unnecessary. In order to be certain that we were dealing with complete branch block, we employed, in some instances, a functional test that is just as conclusive as histological examination. Having obtained what appeared to be complete block in one branch of the bundle, we cut the other branch. If complete heart-block resulted, and if, on macroscopic examination, the second cut was so placed as to make injury to the main stem of the bundle improbable, we regarded the proof that we were in the first instance dealing with unilateral block as complete.

In attempting to divide the left division of the bundle, we had considerable difficulty in properly placing our cuts, and in some instances minor or major subdivisions of this branch were severed while the main stem was not injured. These lesions sometimes produced conspicuous changes in the form of the electrocardiogram, almost invariably, however, of a temporary character: complete, or nearly complete, recovery eventually took place. These temporary changes indicated by their type that they were due to interference with conduction through the left branch as a whole (incomplete left branch block) and not to injury to one or more of its subdivisions. Such changes as were permanent, and could, therefore, be ascribed to section of the subdivisions of the left division, were of a minor character, and were not accompanied by conspicuous widening of the initial deflections.\*

In one instance we were able to cut all those subdivisions of the right bundle branch which bridge the ventricular cavity: the resulting alterations in the form of the ventricular complex were very slight. In another instance, in which the right branch had already been divided, we made a cut on the left side that severed the anterior limb of the left branch near the anterior papillary muscle. The right branch block curves

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\* The temporary changes referred to often persisted for a half-hour or more. We are convinced that the changes in the form of the electrocardiogram which follow attempts to cut the subdivisions of the bundle-branches must be interpreted with great caution. An insignificant injury to the main stem of one of the chief divisions may cause a sufficient shift in the time relation of levoecardiogram and dextroecardiogram to greatly modify the ventricular complex. On the other hand, it is surprising to what an extent the endocardial surface of the septum may be incised and lacerated without permanently altering the form of the ventricular complex. The safest method of studying the effect of lesions of the subdivisions of the bundle-branches is to cut one of the chief divisions, and subsequently the subdivisions of the uninjured branch.

made before this cut were of the concordant type (Fig. 27); those made after the cut were of the discordant type, *Q.R.S.* of lead *I* was upwardly directed, and *T* was negative.\* This result is in accord with the belief expressed by Lewis<sup>3</sup> that the concordant curves of the dog are due to short-circuiting of the ventricular cavity by free strands of conducting tissue. We do not, of course, wish to lay any stress on a single experiment.

*Observations upon notching of Q.R.S. in bundle branch block.* The *Q.R.S.* of left bundle branch block and of right ventricular extrasystoles is almost invariably divided at its summit in axial leads. The time at which the second peak of such curves appears suggests that it is associated with beginning spread of the excitation wave in the left Purkinje plexus. There is a relation, although not a very exact one, between the prominence of this second peak and the prominence of *R'* of the levocardiogram of the same animal. It seems not unlikely, therefore, that the second peak of *Q.R.S.* in left branch block is actually *R'* of the levocardiogram superimposed upon the dextrocardiogram.

This opinion is strengthened by observations upon the behaviour of the second peak of the *Q.R.S.* of right ventricular extrasystoles during such transitions as that shown in Fig. 25. Complex 1 of this figure is a complete right ventricular extrasystole, and its *Q.R.S.* is characteristically double peaked. For convenience in description we may term the first peak *PD* and the second peak *PL*. Complex 2 is a combination of the extrasystolic dextrocardiogram and the normal levocardiogram: in this instance also, *Q.R.S.* is divided at its summit, but *PD* and *PL* are here closer together than in complex 1. Complex 3 shows a still closer approach of the two peaks. In all three complexes, *PD* bears a constant relation to the signal (Table III); as a part of the dextrocardiogram it follows stimulation of the right ventricle by a definite interval. *PL* does not bear a constant relation to the signal but to *P*<sup>†</sup>: it is a part of the levocardiogram. Complexes 1, 2 and 3 are identical in form up to the point at which *PL* appears; *PL* is, therefore, the earliest part of the levocardiogram. It is difficult to avoid the conclusion that *PL* is actually *R'* of the levocardiogram.

The two peaks may be followed farther. In complex 4 they are superimposed and the initial deflection of this complex is, consequently, of greater amplitude than the initial deflections of those which precede it. In complex 5, *PD* precedes *PL* and notches the upstroke of *Q.R.S.* In complexes 6 and 7, the two peaks cannot be distinguished; but in complexes 8, 9, 10 and 11 there appears a thickening of the upstroke of *R*, which signals

\* There was also an increase in the *P-R* interval, indicating injury to the left branch as a whole.

† The levocardiogram of complex 1 does not follow *P*, for in this instance the left ventricular muscle is activated by the excitation wave that crosses the septum from the right side. Nevertheless, the levocardiogram which enters into the formation of this complex must be of the same form as that which enters into the formation of complexes 2 and 3; otherwise, it is difficult to explain the general resemblance of the three complexes.

the further advance of *PL*. In complex 12, the two peaks are again easily distinguishable, but here *PL* is the first and *PD* the second peak: in complex 15, the peaks are widely separated. In the later complexes, the two peaks cannot be distinguished. The measurements upon which our interpretation of Fig. 25 is in part based are given in Table III.

TABLE III.  
*Intervals of Fig. 25.*

Complex.	<i>P-R</i> Int. Seconds.	<i>S-R</i> Int. Seconds.	<i>S-PD</i> * Int. Seconds.
1	0.047	0.031	0.047
2	0.054	0.031	0.047
3	0.052	0.026	0.041
4	0.059	0.026	0.056†
5	0.057	0.028	0.046
6	0.069	0.028	0.052†
7	0.081	0.033	
8	0.084	0.027	—
9	0.084	0.032	—
10	0.085	0.024	—
11	0.085	0.017	—
12	0.085	0.012	0.040
13	0.085	0.013	0.042
14	0.081	0.008	0.041
15	0.084	0.002	0.039
16	0.082	—0.009	0.021‡
17	0.081	—0.010	0.021‡
18	0.084	—0.009	0.022‡
19	0.085	—0.011	0.026‡

From complex 1 to complex 15 the change in outline from complex to complex is slight: these fifteen complexes appear to be combinations in varying time relations of two curves (levocardiogram and dextrocardiogram)

\* The first peak of complexes 1 to 6, the second peak of complexes 12 to 15.

† These complexes have but one peak which is evidently not *PD*.

‡ What appears to be a second peak in these complexes does not bear the same relation to the signal as the second peak of complexes 12 to 15. It is, therefore, not *PD*.

which are essentially the same in form throughout.\* But in complex 16, and more especially in complex 17, a new element seems to have entered the combination. Complex 17 is a fully developed right branch block complex, and the dextrocardiogram which enters into its formation appears to differ in outline from the dextrocardiogram with which we have been dealing in complexes 1 to 15. The deep notch of this complex disappears suddenly, although not completely, in response to a slight change in the time relation of the signal to *P*. Traces of this notch are seen in complexes 16 and 18 to 22, but in no complexes which precede complex 16. We believe that the deep notch of complex 17 represents the spread in the right ventricle of the excitation wave that pierces the septum from the left side. In complexes 16 and 18 to 22 the right ventricular muscle appears to have responded in part to this excitation wave, and in part to the stimulus; the dextrocardiogram of these complexes is a combination of the dextrocardiogram of complex 17 and the extrasystolic dextrocardiogram.

Before we had encountered such conspicuous notching of *Q.R.S.* in right branch block as that shown in complex 17 (Fig. 25), we were inclined to believe that the small notch which frequently occurs on the final limb of *Q.R.S.* in this condition was due to the superimposition of *Q'* of the dextrocardiogram upon the levocardiogram. Such notches are difficult to follow in transitions, for they usually disappear at once when the time relation of levocardiogram and dextrocardiogram is changed (Fig. 9). We cannot positively assert that they belong either to the levocardiogram or to the dextrocardiogram; they seem to occur at the point where the latter begins to be superimposed upon the former.

### *Theory of the T deflection.*

The studies of Lewis and his collaborators<sup>2,3,6</sup> upon the spread of the excitation wave in the heart have given us an analysis of *Q.R.S.* The cause and the mode of origin of the final deflection of the electrocardiogram is still uncertain, the necessary data for the analysis of *T* are still missing. Of the several hypotheses that have been advanced to explain this deflection, that which has gained the most adherents attributes *T* to the decline of the excited state in the ventricular muscle.<sup>4</sup>

It is conceived that the absolute electrical potential of any muscle element during its active period may be represented by some such curve as *ADCD* of Fig. 3. This curve may be divided into three parts: *AB*, a stage of increasing negativity; *BC*, a stage of maintained negativity; and *CD*, a stage of diminishing negativity.

\* The early portions of these curves are identical throughout, but the later portions of the one which precedes the other are deformed. The greater the interval by which one excitation wave precedes the other, the greater the mass of muscle to which it spreads.



Fig. 3. *RS*.—Strip of heart muscle. *Z*.—Right-hand electrode. *C*.—Left-hand electrode. *ABCD*.—Hypothetical time-course of the potential of the muscle under *Z*. *A'B'C'D'*.—Hypothetical time-course of the potential of the muscle under *C*. *IF*.—Theoretical electrogram obtained when the muscle *RS* is stimulated at *R*.

The string galvanometer does not record the absolute potential of one point but the difference of potential between two points. If we place the galvanometer electrodes directly upon a strip of uninjured heart muscle (*RS*) and represent the potential changes of the muscle under the right-hand or *Z*-electrode by the first curve (*ABCD*) of Fig. 3, then we may represent the potential changes of the muscle under the left-hand or *C*-electrode by a second curve (*A'B'C'D'*) of the same form as the first, but separated from it by a time-interval (*AA'*) equal to the time taken by the excitation wave to traverse the muscle between the electrodes.

If, then, the muscle *RS* be stimulated at the end covered by the *Z*-electrode, the curve obtained by subtracting the ordinates of curve *A'B'C'D'* from the ordinates of curve *ABCD* will express the difference in potential between the ends of the muscle during its active period, and, consequently, will be identical with the recorded electrogram.

In this curve ( $IF$ ) there are two deflections: the initial deflection ( $I$ ) is upward, and is produced by unbalanced negativity under the  $Z$ -electrode during the period of activation: the final deflection ( $F$ ) is downward, and is produced by unbalanced negativity under the  $C$ -electrode during the period of deactivation. The duration of the initial deflection is equal to the time taken by the excitation process to advance from the  $Z$ -electrode to the  $C$ -electrode plus the time intervening between beginning negativity under the  $C$  electrode and its full development. The duration of the final deflection ( $F$ ) is equal to the time taken by the excitation process to retreat from the  $Z$ -electrode to the  $C$ -electrode plus the time intervening between beginning loss of negativity and complete loss of negativity under the latter.

The *electrocardiogram* (as opposed to the *electrogram*<sup>1</sup>) is not obtained by placing the galvanometer electrodes directly upon the heart, and is not, therefore, the expression, as is the theoretical curve just described, of the difference of potential between two circumscribed muscle masses. Nevertheless, it is true that  $Q.R.S.$  of the electrocardiogram is produced by forces which are similar in origin to those that give rise to the initial deflection of the curve  $IF$ , and it is believed that  $T$  is similar in origin to the final deflection of this curve.

In comparing  $T$  to the final deflection of the curve  $IF$ , certain assumptions made in drawing Fig. 3 should be borne in mind. Curve  $ABCD$  was drawn arbitrarily.\* The first portion ( $AB$ ) was made a steep upstroke in accordance with the knowledge that the relative negativity of muscle that is passing into the active state develops very quickly. The second horizontal portion ( $BC$ ) assumes that, for a period of its activity, a muscle element remains at the same potential: there is no evidence indicating whether this is or is not true.\* The third portion ( $CD$ ) was made a gradual decline in order to account for the long duration of  $T$  as compared with the short duration of  $Q.R.S.$  Curves  $ABCD$  and  $A'B'C'D'$  were made identical in form: that is, we assumed that all parts of a muscle remain in the excited state the same length of time and that during this time they pass through exactly the same phases of activity in the same relation to each other. In drawing these curves of the same amplitude, we assumed further that the forces developed under the two electrodes are of the same magnitude.

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\* The first curve of this form was drawn by Sanderson and Page.<sup>11</sup> It was based upon the monophasic curve obtained when the galvanometer electrodes are placed directly upon the frog's heart<sup>12</sup> the  $Z$ -electrode upon an uninjured spot and the  $C$ -electrode upon a spot injured by heat. It is quite generally agreed by physiologists<sup>1</sup> that this monophasic curve represents the electrical activity of the muscle under the  $Z$ -electrode. We have not been able to find published monophasic curves obtained by this method from the mammalian heart, but they might be expected to resemble those obtained from the heart of the frog in general outline. We have avoided introducing conclusions based upon the curves obtained by direct leads, because we feel that the factors that determine their form are as yet imperfectly understood, and have, until recently, been little appreciated.<sup>6</sup>

*Relations between the form of T and the form of Q.R.S. and between the R-T interval and the Q.R.S. interval.*

If the *T* deflection is produced by the decline of the excited state in the ventricular muscle, and if all portions of the ventricular muscle remain in the excited state for the same length of time, there should be a definite relation, for any given heart, between the form of *T* and the form of *Q.R.S.*; for the order in which the various regions of the ventricular muscle pass into the excited state will determine the order in which they pass out of the excited state.

That there is some relation between the form of *Q.R.S.* and the form of *T* will, we believe, be admitted by everyone who has had occasion to study many electrocardiographic curves. But that there is a very exact relation of this kind in the curves taken in a single lead from a single heart, we did not fully realise until we began to combine the levocardiogram and dextrocardiogram experimentally. In Fig. 10, it will be seen that every change in *Q.R.S.* is accompanied by a corresponding change in *T* of opposite sign. In the early complexes of this figure, *Q.R.S.* is upright and of large amplitude: *T* is negative and of correspondingly great amplitude. As *Q.R.S.* becomes shorter, *T* becomes less negative, and when the chief deflection of *Q.R.S.* becomes negative, *T* becomes positive. The same relation of *T* to *Q.R.S.* is shown in Figs. 9 and 25. Now the form of *Q.R.S.* is determined by the order and direction in which various regions of the ventricular muscle are activated. Assuming that *T* is produced by the decline of the excited state, then the relation displayed between the form of *T* and the form of *Q.R.S.* would seem to indicate that the order of deactivation is the same as the order of activation, but that the forces produced by the two processes are oppositely directed. If one part of the ventricular muscle remained in the excited state a considerably longer time than other parts, the relation that exists between the form of *T* and the form of *Q.R.S.* would be difficult to explain.

The assumption that the duration of the excited state is uniform throughout the ventricular muscle may be tested in another way. If one region remains in the excited state longer than all other regions, the *R-T* interval should depend to some extent upon whether this region is activated early or late, and, therefore, upon the form of *Q.R.S.* If, on the other hand, the duration of the excited state is the same for all parts of the ventricular muscle, the *R-T* interval should be equal to the *Q.R.S.* interval plus a constant. In other words, every change in the *Q.R.S.* interval should be accompanied by a corresponding change in the *R-T* interval in spite of simultaneous changes in the form of *Q.R.S.* The *Q.R.S.* intervals and the *R-T* intervals of Fig. 10 are given in Table IV.

It will be seen that there is a relation between the *Q.R.S.* interval and the *R-T* interval; with one minor exception, each increase or decrease of the former is accompanied by a corresponding increase or decrease in the latter. Nevertheless, the changes in the *Q.R.S.* interval are not numerically equal to the changes in the *R-T* interval, and if we compare complex 1 in



TABLE IV.  
*Q. R.S. intervals and R-T intervals of Fig. 10.*

Complex.	<i>Q. R.S. Int.</i> Seconds.	<i>R-T Int.</i> Seconds.	Change in <i>Q. R.S. Int.</i> Seconds.	Change in <i>R T Int.</i> Seconds.
1	0.067	0.238	—	—
2	0.048	0.216	—0.019	—0.022
3	0.043	0.208	—0.005	—0.008
4	0.049	0.210	0.006	0.002
5	0.073	0.226	0.024	0.016
6	0.078	0.224	0.005	—0.002

which *Q. R.S.* is positive with complex 6 in which *Q. R.S.* is negative, we find that although the *Q. R.S.* interval of the former is 0.011 second shorter than the *Q. R.S.* interval of the latter, its *R-T* interval is 0.014 second longer. There is some difficulty, of course, in locating the end of *Q. R.S.* and the end of *T* accurately, and furthermore, the *R-T* interval varies slightly even when the cardiac mechanism is constant. We have measured other curves of the same type as Fig. 10, and these showed a similar relation between the *Q. R.S.* and *R-T* intervals to that shown in Table IV. We believe that these results indicate that there may be a difference in the duration of the excited state in different regions, but if so, it is not of high degree.

*The refractory period of the heart in bundle branch block.*

In order to obtain more certain evidence upon the uniformity of the duration of the excited state in different regions, we determined the time at which the refractory period ends at various points on the ventricular surface, and compared the order in which various regions of the ventricular muscle pass out of the refractory state with the order in which they are known to become active.

By the method of rhythmic stimulation previously described, we were able to place stimuli in all parts of the cardiac cycle. When the rate of stimulation is just a little slower than the heart rate, each stimulus falls a little later in the cardiac cycle than its predecessor. If we begin with a stimulus that falls in the refractory period, each succeeding stimulus falls nearer the end of this period until finally a response occurs. The end of the refractory period\* of the point tested is then known to fall later in

\* The length of the refractory period depends to a certain extent upon the strength of the stimulus: the refractory period to a weak stimulus is longer than that to a strong stimulus. If the strength of the stimulus is gradually increased, however, a point is reached beyond which a further increase in the stimulus produces no change in the refractory period. The period during which no response can be produced, whatever the strength of the stimulus, is called the absolute refractory period.<sup>1</sup> In our experiments, we used strong stimuli in order to avoid possible effects of slight variations in the strength of the stimulus.



the heart cycle than the latest stimulus that fails to produce a response and earlier than the earliest stimulus that produces a response. By adjusting the rate of stimulation with sufficient care and by multiplying the number of records taken, the point in the heart cycle at which the refractory period ends may be determined as accurately as is desirable.

It is obviously easier by the method described to determine great differences in the refractory period of different regions than small differences. We began our experiments, therefore, upon animals in which bundle branch block had been produced. Fig. 11 illustrates the method. The right branch of the bundle was cut. The top curve shows the effect of rhythmic stimulation of the apex of the left ventricle: the refractory period ended between 0.165 and 0.179 second after *Q*. The bottom record shows the effect of rhythmic stimulation of the conus of the right ventricle: the refractory period ended between 0.200 and 0.210 second after *Q*.

It was our desire in these experiments to compare the refractory period of points on the surface of the right ventricle with the refractory period of points on the surface of the left ventricle. In order, therefore, to avoid the effect of changes in heart rate and other factors which, being known to affect the duration of the excited state, probably also influence the duration of the refractory period, we usually tested two points, one on the surface of each ventricle, in quick succession. It is for this reason that, in the tables given, we have arranged the determinations in the order in which they were made. Determinations upon right and left ventricular points which bear the same or consecutive curve numbers were made as close together as possible, and are of more value for comparison than determinations separated by greater intervals.

*Experiment 12.* The results of experiment 12 are given in Table V.

TABLE V.

*Experiment 12. Right bundle branch block.*

No. of curve.	Region tested.	Seconds after <i>Q</i> .	
		Earliest effective stimulus.	Latest ineffective stimulus.
1288	R. conus . . . . .	0.219	0.1895
1288	L. apex . . . . .	0.174	0.151
1289	R. conus . . . . .	0.210	0.200
1289	L. apex . . . . .	0.179	0.165
1290	R. conus . . . . .	—	0.203
1290	L. apex . . . . .	0.181	—
1294	R. trabeculated area . . . . .	0.1675	0.160
1295	R. conus . . . . .	—	0.185
1295	L. apex . . . . .	0.168	0.154
1295	R. trabeculated area . . . . .	0.174	0.153

The names used in the second column (Table V) to designate various regions are those employed by Lewis<sup>5</sup>: the location of each region referred to is shown in Fig. 4. We give for each point tested the intervals by which the earliest stimulus that produced a response, and the latest stimulus that failed to produce a response, followed some chosen point of *Q.R.S.* The earliest effective stimulus and the latest ineffective stimulus could usually

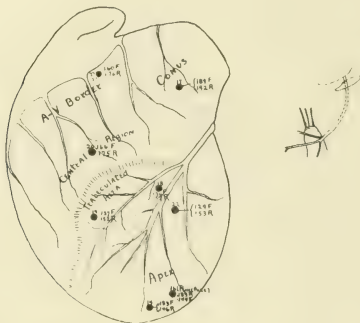


Fig. 4. Outline drawing of the anterior surface of the heart of Dog 15. Black dots indicate points tested. Numbers above dots are curve numbers. Numbers to the right of dots indicate the intervals by which the earliest effective stimulus (*R*) and the latest ineffective stimulus (*F*) followed the peak of *R'*. Small drawing on the right shows the location of the cut with reference to the right division of the His-bundle.

be identified on inspection of the curves by the relation of the signals to the apex of *T*. In some instances only one measurement is given; in such cases the earliest effective stimulus or the latest ineffective stimulus obviously fell so far from the end of the refractory period that the second measurement would have been of no value.

Table V shows that in experiment 12 (right branch block) the refractory period of points on the right conus outlasted the refractory period of points on the left apex by between 0.02 and 0.03 second. The trabeculated area recovered its excitability little if any later than the left apex.

*Experiment 15* (right branch block) is summarised in Table VI.

TABLE VI.

*Experiment 15. Right bundle branch block.*

No. of curve.	Region tested.	Seconds after peak of <i>R'</i> .	
		Earliest effective stimulus.	Latest ineffective stimulus.
1511	L. apex - - -	0.146	0.133
1516	L. apex (deep layers) - -	0.135	0.144
1517	R. conus - - -	0.192	0.189
1518	R. trabeculated area* - -	0.157	0.136
1519	R. trabeculated area - -	0.152	0.137
1520	R. central region - - -	0.175	0.166
1521	R. A-V border - - -	0.176	—
1522	L. anterior surface - - -	0.153	0.129
1523	R. A-V border - - -		0.160
1526	L. apex (deep layers) - -	0.121	-
1526	L. apex (deep layers) - -	0.128	—

The location of the points tested is shown on an outline drawing of the anterior surface of the heart sketched at the time of the experiment (Fig. 4). The conus recovered about 0.04 second later than the left apex. The right central region and the right A-V border recovered about 0.02 to 0.03 second later than the left apex. The trabeculated area and the left apex recovered at about the same time. In this experiment we also tested the deeper layers of the apical muscle: the platinum points were thrust into the apex to a depth of 8 mm., and it was found that at this depth the refractory period ended between 0.01 and 0.02 second earlier than at the surface in the same region. It will be noted that the figure for the latest ineffective stimulus of curve 1516 is greater than the figure for the earliest effective stimulus. Discrepancies of this kind occasionally occurred: their cause is unknown to us. In this particular instance the curves were developed as soon as they were made and the discrepancy was noted. The deeper layers of the apex were tested a second time (1526), and the result showed that the figure for the earliest effective stimulus of curve 1516 is correct.

\* The location of this point is shown in Fig. 4. The complexes obtained were of the right ventricular type.

Experiment 16 is summarised in Table VII.

TABLE VII.  
Experiment 16.

No. of curve.	Region tested.	Seconds after $R'$ .	
		Earliest effective stimulus.	Latest ineffective stimulus.
<i>Left bundle branch block.</i>			
1638	R. conus . . . . .	0.178	0.166
1639	L. apex . . . . .	0.215	0.1965
1642	R. conus . . . . .	0.164	0.148
1643	L. apex . . . . .	0.197	0.188
1644	R. central region . . . . .	0.164	0.152
1645	R. trabeculated area . . . . .	0.153	0.140
1646	L. apex . . . . .	0.185	0.181
1647	R. conus . . . . .	0.169	0.1525
<i>Right bundle branch block.</i>			
1652	R. conus . . . . .	0.196	0.176
1653	L. apex . . . . .	0.160	0.152
1654	R. conus . . . . .	0.177*	0.168
1655	L. apex . . . . .	0.165	0.143
1656	R. central region . . . . .		0.186
1657	L. apex (deep layers) . . . . .	0.150	0.141
1658	R. trabeculated area . . . . .	0.174	0.1615

In this experiment we attempted to cut the left branch of the bundle, and left branch block resulted. It persisted sufficiently long for the examination of a number of points, and then recovery took place. We then cut the right branch of the bundle and re-examined the points previously tested.

While left branch block was present, the surface of the right ventricle recovered in advance of the surface of the left. The right conus recovered about 0.03 second in advance of the left apex. The trabeculated area appeared to recover a little earlier than the conus.

\* This figure should probably appear in the other column. Right ventricular extrasystoles were occurring spontaneously when this curve was made.

While right branch block was present, the surface of the left ventricle recovered in advance of the surface of the right. If we disregard the figure 0.177 for the earliest effective stimulus of curve 1654 (for the reason stated in the table this figure is probably incorrect) the conus region and the right central region recovered 0.02 or 0.03 second later than the left apex. The trabeculated area recovered at about the same time as the apex. The deeper layers of the apex (8 mm. deep) recovered at least 0.01 second earlier than the surface layers.

*Experiment 17* is summarised in Table VIII.

TABLE VIII.  
*Experiment 17.*

No. of curve.	Region tested.	Seconds after <i>R</i> .	
		Earliest effective stimulus.	Latest ineffective stimulus.
<i>Left bundle branch block.</i>			
1765	R. conus	0.133	—
		0.137	—
1765	L. apex	0.160	0.159
1767	L. apex	—	0.150
<i>Right bundle branch block.*</i>			
1770	L. apex	0.145	0.128
1770	R. conus	—	0.150
1772	R. central region	—	0.162
1773	L. apex (deep layers)	0.114	—
1774	R. trabeculated area	0.137	—

In this experiment also the cut on the left side of the septum produced temporary left branch block. The left branch recovered completely, and we were able, therefore, to obtain right branch block as well as left. In this instance the free strands of the right branch that bridge the ventricular cavity were cut as well as the main stem of this division. The results obtained are similar to those of experiment 16. While left branch block was present, the right conus recovered in advance of the left apex. While right branch

\* In this experiment the free strands of the right branch which bridge the ventricular cavity were cut as well as the main stem of the right branch.

block was present, the relation of these regions was reversed. The deeper layers of the apex (8 mm. deep) recovered in advance of the surface layers.

*Relation of the end of the refractory period to T.* The measurements given in Tables V, VI, VII and VIII show numerically the order in which various regions of the anterior surface of the ventricles pass out of the refractory state, but they do not indicate the relation of the earliest effective stimulus to the phases of *T*, a relation which is one of the most striking features of the records.

In right branch block *T* is positive. When the surface of the left ventricle was stimulated, the earliest effective stimulus fell very close to the apex of *T*. When the surface of the right ventricle was stimulated, the earliest effective stimulus fell near the end of *T*. When the deeper layers of the left apex were stimulated, the earliest effective stimulus preceded the apex of *T*; often by a considerable interval.

In left branch block *T* is negative. When the right ventricle was stimulated, the earliest effective stimulus fell near and usually preceded the point of greatest negativity. When the left ventricle was stimulated, the earliest effective stimulus fell on the final limb of *T* and usually near its end.

*Simultaneous stimulation of two points.* The method of comparing the refractory period of right and left ventricular points, already described, has certain disadvantages. If the heart rate is not constant, it is difficult to adjust the rate of stimulation so as to determine the refractory period within narrow limits without taking a large number of records. Furthermore, an interval elapses between the testing of one point and the testing of the point with which it is to be compared, and during this interval changes in heart rate or other factors may affect the length of the refractory period. To overcome these difficulties we adopted a slightly different method in our later experiments. Two electrodes were attached to the induction coil instead of one, and the two points to be compared were stimulated simultaneously. The two electrodes were identical in form; separation of the platinum points, and other particulars. The usual procedure was as follows: One electrode was placed on the surface of the right ventricle and a curve was taken; without removing this electrode the second electrode was placed on the surface of the left ventricle and a second curve was taken; and finally, the first electrode was removed, the second being allowed to remain, and a third curve was taken. The first and third records were made for the purpose of determining the form of the ventricular complex produced by stimulation of each of the two points to be compared. Most of the extrasystolic complexes of the second record were of combination form; they were produced by the algebraic summation of the extrasystolic dextrocardiogram and the extrasystolic levocardiogram. The earliest effective stimulus, however, usually found one of the two points

still in the refractory state; if the right ventricular point recovered first, the resulting ventricular complexes was of the same form as the extrasystolic complexes of the first curve of the series; if the left ventricular point recovered first, the resulting ventricular complex was of the same form as the ventricular complexes of the last curve of the series.

Fig. 13 (Exp. 18) illustrates the method. Right bundle branch block was present. The top curve shows the effect of rhythmic stimulation of the conus region: the earliest effective stimulus fell near the end of *T*. The middle curve shows the effect of rhythmic stimulation of the left apex: the earliest effective stimulus fell near the apex of *T*. The bottom curve shows the effect of simultaneous stimulation of conus and apex: the earliest effective stimulus fell near the apex of *T* and produced a complex identical in form with that obtained by stimulation of the apex alone. All later stimuli produced complexes of combination form. This curve confirms the conclusion that the apex recovered in advance of the conus in a very graphic way.

It should be pointed out that, even when a single point is stimulated, the complex that follows the earliest effective stimulus differs slightly in form from those that follow later stimuli (Fig. 13); it is usually of greater amplitude as regards both *Q.R.S.* and *T*. The mechanical response which follows the earliest effective stimulus is said to be also of unusually large amplitude, and this has been attributed to an especially favourable H-ion concentration at this point in the heart cycle. There is, of course, no definite relation between the amplitude of the mechanical response and the amplitude of the electrocardiographic deflections. The differences in form between the complex of the earliest forced cycle and the complexes of later forced cycles makes it desirable to test each of the chosen points separately before stimulating them simultaneously.

*Other illustrations.* Fig. 16 shows the effect of simultaneous stimulation of the right central region and the left apex in left branch block: the earliest effective stimulus produced a right ventricular extrasystole; later stimuli produced combined complexes.

In this experiment (22) we were able to obtain both left and right branch block: while the former was present, the right central region recovered in advance of the left apex (3rd curve of Fig. 16); while the latter was present, comparison of the same two regions showed that the left apex recovered first (4th curve of Fig. 16).

The method of simultaneous stimulation may also be used to determine the interval by which one point precedes the other in recovery. In Exp. 23 (left branch block) simultaneous stimulation of the right central region and the left apex showed that all stimuli that fell between 0.1807 and 0.2394 second after *Q'* produced right ventricular extrasystoles. We conclude, therefore, that the right central region recovered nearly 0.06 second earlier than the left apex.

A summary of the results obtained by simultaneous stimulation of right and left ventricular points in right and left branch block is given in Table IX.

TABLE IX.

*Results of simultaneous stimulation of right and left ventricular points in bundle branch block.*

No. of experiment.	Bundle injured.	Location of right vent. point.	Location of left vent. point.	Point that recovered first, right or left.
18	Right	Central region	Apex	Left
19	Left	Central region	Apex	Right
21	Right	Central region	Apex	Left
21	Right	Trabeculated area	Apex	Right
22	Right	Central region	Apex	Left
22	Left	Central region	Apex	Right
23	Left	Central region	Apex	Right
30	Right	Central region	Apex	Left
30	Right	Trabeculated area	Apex	Left

It will be seen that in all instances except one the point on the side on which the bundle branch was injured recovered later than the point on the opposite side with which it was compared. The single exception occurred in experiment 21; in this instance the trabeculated area recovered in advance of the left apex, although the right branch was cut. We have already pointed out that the trabeculated area recovers early in right branch block.

*Summary of branch block experiments.* In right branch block the anterior surface of the left ventricle passes out of the refractory state 0.02 to 0.04 second in advance of the anterior surface of the right ventricle. The trabeculated area passes out of the refractory state at about the same time as the surface of the left apex. The deeper layers of the left apex pass out of the refractory state in advance of the surface layers. The left ventricular surface passes out of the refractory state at about the time that the apex of *T* is written. The right ventricular surface does not recover its excitability until *T* is nearly complete.

In left bundle branch block the surface of the right ventricle recovers its excitability 0.02 to 0.06 second in advance of the surface of the left ventricle. The right ventricular surface passes out of the refractory state at about the time that *T* reaches its point of greatest negativity; the left ventricular surface does not recover until *T* is nearly complete.

*Refractory period of the heart when the cardiac mechanism is normal.*

When we began to study the refractory period of the normally beating heart, as we had previously studied the refractory period in bundle branch



block, we soon discovered that the differences in the times of recovery of various regions were small. It was difficult, therefore, to determine which of two points recovered first by testing them separately. In some instances, however, we were able by this method to show that the right central region recovered in advance of the left apex. Fig. 14 illustrates this point. The refractory period of the right central region (top curve) ended between 0.122 and 0.141 second after *R*. The refractory period of the left apex ended between 0.146 and 0.161 second after *R* (bottom curve).

The method of simultaneous stimulation was more serviceable. We usually compared points in the right central region with points on the left apex and with the deeper layers of the left apex. The usual procedure was as follows: The first electrode was placed on the right central region and a curve was taken; the second electrode was placed on the left apex (the first electrode being allowed to remain in place) and a second curve was taken; without changing the position of either electrode, the second electrode was thrust into the apical musculature as far as the length of the platinum points permitted, and a third curve was taken; the first electrode was removed, and a fourth curve was taken. In some instances the first and fourth records of this series were not made.

Fig. 15 illustrates the method. When the surface of the right central region and the surface of the left apex were compared, the right central region recovered first (top curve). When the electrode on the apex was thrust into the deeper layers of muscle, however, it was found that the deeper layers of the apex recovered in advance of the right central region (middle curve).

A second example is given in Fig. 16. In this instance also the surface layers of the right central region recovered in advance of the surface layers of the left apex, but the deeper layers of the apex recovered earlier than the right central region.

Similar results were obtained in all experiments. In one instance we tried the effect of thrusting the right ventricular electrode into the deeper layers of the right central region; the electrode pierced the heart wall, and curiously enough it struck and injured the right branch of the His-bundle. Temporary right branch block resulted (Fig. 15 bottom curve).

Table X summarises our experiments upon the normally beating heart. The right central region was compared with the left apex in 13 experiments; in 11 instances the right central region recovered first; in one instance the left apex recovered first; and in one instance the difference in the times of recovery was so small that it could not be detected. The deeper layers of the left apex were compared with the surface of the right central region in 10 experiments; in nine of these the deeper layers of the apex recovered first; in one instance the right central region recovered first. In one experiment the deeper layers of the right central region were compared with the surface of the left apex; most of the early stimuli

produced complexes of combination form: one very early stimulus produced a left ventricular extrasystole. The last observation was made in an experiment in which the surface of the left apex recovered in advance of the surface of the right central region. So far as tested, the right A-V border and the right conus recovered in advance of the left apex, except that in one instance a point in the immediate neighbourhood of the pulmonary valves recovered later than the left apex.

TABLE X.

*Summary of experiments upon the normally beating heart.*

No. of experiment.	Location of right ventricular point.	Location of left ventricular point.	Point which recovered first, right or left.
19	Central region	Apex	Right
	Central region	Apex (deep layers)	Left
20	Central region	Apex	Left
	Central region	Apex (deep layers)	Left
	Central region (deep layers)	Apex	Left
21	Central region	Apex	Right
	Central region	Apex (deep layers)	Left
22	Central region	Apex	Right
	Central region	Apex (deep layers)	Left
23	Central region	Apex	Right
	Central region	Apex (deep layers)	Left
	Conus	Apex	Right
	A-V border	Apex	Right
	Conus near pul. valves	Apex	Left
24	Central region	Apex	Right
	Conus near pul. valves	Apex	Right
	Conus near pul. valves	Apex (deep layers)	Left
26	Central region	Apex	Right
27	Central region	Apex	Right
	Central region	Apex (deep layers)	Right
28	Central region	Apex	?
	Central region	Apex (deep layers)	Left
29	Central region	Apex	Right
	Central region	Apex (deep layers)	Left
30	Central region	Apex	Right
31	Central region	Apex	Right
	Central region	Apex (deep layers)	Left
32	Central region	Apex	Right
	Central region	Apex (deep layers)	Left

To sum up: in the majority of dogs, the surface of the right central region, and probably all of the anterior surface of the right ventricle, except perhaps the region in the immediate neighbourhood of the pulmonary valves, passes out of the refractory state in advance of the surface of the left apex. The deeper layers of the left apex usually recover earlier than the surface of the right central region, and always recover earlier than the surface layers of the left apex.

*Comparison of the order in which various regions pass out of the refractory state with the order in which they are known to pass into the excited state.*

When we compare the order in which various regions pass out of the refractory state with the order in which they are known to become active, we are struck by a great similarity. Lewis and Rothschild<sup>5</sup> found that when the right branch of the His-bundle was cut, the activation of the right ventricular muscle was greatly delayed. They publish<sup>5</sup> outline drawings of two hearts showing the order of excitation at the ventricular surface before and after section of the right division of the bundle. Following the cut, the readings at right ventricular points rose about 0.04 second, so that they exceeded readings at left ventricular points by 0.03 to 0.05 second. Readings in the trabeculated area also rose, but not to the same extent; even after the cut they were but little higher than readings in the apex region. When the cardiac mechanism was normal they found<sup>5</sup> that the right central region was usually the first part of the ventricular surface to become active; in a few instances the extreme apex was almost as early. The endocardial surface of the apex preceded the epicardial surface by 0.01 or 0.02 second. The surface of the conus region passed into the excited state relatively late; always later than the right central region, and often later than the anterior surface of the left ventricle.

Turning now to our study of the refractory period, we find that in right branch block the anterior surface of the right ventricle recovers about 0.03 to 0.04 second later than the anterior surface of the left ventricle. The trabeculated area recovers at about the same time as the left apex. When the cardiac mechanism is normal, the right central region almost always recovers earlier than the anterior surface of the left ventricle. The deeper layers of the left apex that lie near the endocardium recover 0.01 to 0.02 second earlier than the surface layers overlying them. We have not been able to demonstrate, conclusively, that the conus region is relatively late in comparison with the right central region although some of our readings suggest that this is the case.

The order of recovery is, therefore, almost exactly the same as the order of excitation. Assuming that the refractory period bears a constant relation to the period of excitation, the results of our experiments indicate that, under the conditions of the experiments, the duration of the excited state is approximately uniform in all parts of the ventricular muscle.\*

*A conflicting experiment.* We have inserted the word approximately in our conclusion for two reasons: first, because the duration of the refractory period is influenced, as we shall show later, by factors that do not appear to influence the order of excitation; and second, because of an experiment illustrated in Fig. 23. These curves were obtained during

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\* We have tested only the anterior surface of the heart, but we believe that it is safe to assume that the other surfaces behave in a similar fashion.

simultaneous stimulation of the right central region and the left apex. In this instance an error in adjusting the stimulating apparatus resulted in placing a make shock in the middle of each second inter-break shock interval. In consequence, right ventricular extrasystoles occurred in couples: the first member of the couple was due to the response of the right ventricular point to the interpolated make shock: the second member of the couple was due to a response to the following break shock. Now the previous break shock had stimulated both points at the same instant, and both had had the same time to recover before the interpolated make shock occurred. Only the right ventricular point recovered in this time, and its refractory period must, therefore, have been slightly shorter than that of the left ventricular point. The difference was probably not great, for in some instances the make shock found both points in the refractory state: apparently the refractory period of the right ventricular point varied a little in length. The break shock that followed the interpolated make found only the right point excitable: this point was thrown into the excited state earlier than the left point, and had had a greater length of time to recover. We did not attempt to repeat these observations and do not know that the results obtained were not due to factors peculiar to this experiment alone. The difference in the duration of the refractory period at the right central region and at the left apex noted in this single instance was too slight to invalidate our general conclusions.\*

The lower right hand curve of Fig. 23 shows the effect of reducing the strength of the stimulus. The make shock is less effective than the break shock, and when we reduced the strength of the stimuli sufficiently to bring the interpolated make below threshold value, we found that, right branch block being present, the left apex recovered in advance of the right central region, but both regions recovered relatively late. The earliest effective stimulus fell near the end of  $T$  and found only the left apex excitable. This observation indicates that the order of recovery is the same for weak as for strong stimuli. It should be pointed out that the stronger the stimulus, the deeper the muscle layers reached by stimuli of threshold value: some part of the difference between the refractory period to weak and that to strong stimuli may be due to this cause. It should also be remembered that only a comparatively small mass of muscle is directly affected by the stimulus: distant regions are activated by a propagated disturbance, the magnitude of which can hardly depend upon

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\* When we discovered (see later section of this article) that cooling the ventricular surface prolonged the refractory period of the region cooled, we began to wonder whether local cooling played any part in this experiment, and also whether it played a part in our other experiments, especially those which compared the refractory period of the surface layers of the apex with that of the deeper layers, and those that were concerned with a comparison of the refractory period of the thin-walled right ventricle with that of the thick-walled left ventricle. We repeated our previous experiments, trying by various methods to rule out this factor, and got the same results as before. These later experiments, and the general uniformity of our results, lead us to believe that local cooling played no appreciable part in producing the observed differences in the time of recovery of various regions.

the strength of the stimulus. The existence of a relative as well as an absolute refractory period is difficult to understand unless the propagated disturbance is conducted more slowly at the time when the absolute refractory period ends than it is later : or unless the propagated disturbance is always of sufficient magnitude to excite all regions that have passed out of the absolute refractory period.

*The effect of local cooling upon the refractory period and upon the form of the T deflection.*

It has been shown repeatedly<sup>13</sup> that the application of cold or heat to the surface of the ventricles produces changes in the form of the end phase of the electrocardiogram. The character of these changes is shown in Fig. 26, which depicts the effect in each of the three leads of spraying the posterior wall of the left ventricle with ethyl chloride. The heart was lifted up from the pericardial sac and the cooling agent was sprayed over the posterior basal surface; the heart was then replaced and a curve was taken. The effect was transient, and the spraying had to be repeated for each lead. In each instance there was no change in *Q.R.S.*, but *T* became very much more negative than in the control curve. We attempted in several experiments to determine the relation between the area cooled and the type of change in *T* that took place. In general, we got the same results as previous investigators<sup>13</sup>; cooling the apex of the left ventricle made *T* more negative in all leads; cooling the right base often produced comparatively little effect, but when *T* was changed it became more positive in axial leads. Cooling other portions of the anterior surface of the left ventricle produced much the same effect as cooling the apex. In one instance cooling the apex of the right ventricle made *T* more negative on leads *II* and *III* and more positive in lead *I*.

We do not wish to lay any particular stress upon these results because we are uncertain as to the exact extent of the region cooled. The spray produces a mist all about the point of application, and not all of the ethyl chloride evaporates immediately; some trickles down into the pericardial sac. It seems likely that the region of effective cooling is considerably larger than the small area to which the spray is directly applied. The same criticism applies in varying degree to most methods so far employed for determining the effect of changing the temperature of the ventricular surface locally upon the form of *T*.\*

In a number of experiments we determined the effect of local cooling upon the refractory period. In every instance the refractory period of

\* We speak here of *T* of the electrocardiogram, and not of the end-phase of curves obtained by direct leads. In the latter case the extent of the cooled area is not of great importance so long as the muscle lying under one electrode is cooled and that lying under the other is not. In curves taken in this way, however, it is not always easy to distinguish between extrinsic and intrinsic effects.<sup>6</sup>

the region to which the ethyl chloride was applied was greatly prolonged. Fig. 24 shows the effect of cooling the left apex upon the refractory period of the same region: the refractory period was increased in length by at least 0.06 second. It is interesting that the cooling affected the normal  $T$  and the extrasystolic  $T$  in similar ways: the normal  $T$  was made more negative, the extrasystolic  $T$  was made less positive. No part of the extrasystolic  $T$  was unaffected. In the same experiment, cooling the left apex did not affect the refractory period of the right central region. In this instance both the normal  $T$  and the extrasystolic  $T$  were made more negative. When the anterior basal surface and the right central region of the right ventricle were cooled, the refractory period of the right central region was definitely increased in length. The negative  $T$  of the normal complex became positive and  $T$  of the extrasystolic complex became less negative. Similar results were obtained in all other experiments.

In a few experiments we tested the effect of local cooling upon the refractory period by the method of simultaneous stimulation. The results are summarised in Table XI. It will be seen that when surface points were compared, the uncooled point always recovered first. Cooling the left apex produced so great a delay in its recovery, that it was preceded by the right central region after section of the right branch of the His-bundle. Cooling the left apex had no appreciable effect upon the time of recovery of the deeper layers of muscle that lie near the endocardium.

TABLE XI.

*The refractory period of local cooling upon the refractory period of the region cooled.*

No. of experiment.	Cardiac mechanism.	Regions compared.	Point that recovered first.
26	Normal	R. central and L. apex (control)	Right
		R. central and L. apex after cooling R. central	Left
	R. branch block	R. central and L. apex after cooling L. apex	Right
27	Normal	R. central and L. apex	?
		R. central and L. apex after cooling L. apex R. central and L. apex (deep layers) after cooling L. apex	Right Left
31	R. branch block	R. central and L. apex (control)	Left
		R. central and L. apex after cooling L. apex R. central and L. apex (deep layers) after cooling L. apex	Right Left
32	Normal	R. central and L. apex (deep layers)	Left
		R. central and L. apex (deep layers) after cooling left apex	Left

To sum up\*: Cooling the surface of the ventricles greatly prolongs the refractory period of the surface layers of muscle in the region cooled: it does not affect the refractory period of the deeper layers (8 mm. deep). Cooling the ventricular surface does not affect the form of *Q.R.S.*, but may change the form of *T* profoundly. It is easier to affect *T* by cooling the surface of the left ventricle than by cooling the surface of the right: the right apex is a possible exception to this rule. Cooling a given region changes the normal and the extrasystolic *T* in the same direction. When *T* is modified by cooling the ventricular surface, it is modified in all its parts, early and late: the extrasystolic *T* is modified from its beginning at the end of *Q.R.S.* to the end of the ventricular complex.

#### *A partial analysis of T.*

The *T* deflection may now be examined in the light of the new facts that have been accumulated. Is *T* the result of the decline of the state of excitation in the ventricular muscle? In attempting to answer this question we may ask whether the writing of *T* and the decline of the state of excitation take place at the same time, whether they are of the same duration, and whether modification of the one is accompanied by modifications of the other.

#### *Relation of the refractory period to the state of excitation.*

We have attempted to follow the retreat of the excitation process by studying the refractory period. Unfortunately the exact relation of the refractory period to the excited state is not known.† There is considerable evidence that the refractory period begins simultaneously with the state of excitation. *Q.R.S.* is known to be due to the spread of the excitation process: when *Q.R.S.* is complete all of the ventricular muscle is active and all of the ventricular muscle is in the refractory state. In right branch block the first part of *Q.R.S.* is due to the spread of the excitation process in the muscle of the left ventricle: the right ventricular muscle does not pass into the excited state until 0.04 or 0.05 second after *Q.R.S.* begins. In right branch block the right ventricular muscle is still excitable after

\* It is unfortunate that we used ethyl chloride as a cooling agent in these experiments: it has been pointed out to us that the anæsthetic action of ethyl chloride must be considered as well as its cooling action. Smith did not note any difference between the effect of ethyl chloride and that of other cooling agents upon the form of *T*. The statement is made in Bayliss' *Physiology* that narcotics such as alcohol, ether, etc., have the property of rendering tissues temporarily irresponsive to stimuli (page 138). Lucas\* found that alcohol did not affect the refractory period of nerve.

† According to Keith Lucas\* the refractory period of the heart muscle of the frog does not end until the monophasic response is complete. In his experiments the capillary electrometer was used: the Z-electrode was placed upon an uninjured spot at the ventricular base and the C-electrode upon an injured spot at the ventricular apex. The stimulus was applied to the auricle or to the ventricular base. If, under these conditions, the monophasic response represents the electrical activity of the muscle under the Z-electrode it is difficult to understand why the relation of the end of the refractory period to the recorded curve does not vary with the point stimulated. From Lewis's analysis of the spread of the excitation process in the toad's heart we should anticipate that stimulation of the auricle and stimulation of the ventricular base would not give the same results. We have not felt justified in concluding from the work of Lucas that the refractory period ends at *D* of curve *ABCD* (Fig. 3) rather than at *C*.



the first part of *Q.R.S.* has been written, for stimulation of the right ventricle during the first part of the *Q.R.S.* interval modifies the form of the ventricular complex; stimulation of the left ventricle at this time does not (Fig. 10). In left branch block, on the other hand, the right ventricle passes into the refractory state in advance of the left. It is fairly certain, then, that the refractory period and the state of excitation begin at the same time.

It is also quite evident that the end of the refractory period is associated with the termination of the state of excitation; for lack of excitability is one of the chief characteristics that distinguishes excited tissue from quiescent tissue. The chief difficulty is that we do not know whether the excitability of heart muscle returns immediately the state of excitation has begun to decline, when the state of excitation has entirely disappeared, or at some intermediate point. Referring again to curve *ABCD* of Fig. 3, we do not know whether the absolute refractory period ends at *C*, at *D*, or at some point between *C* and *D*. The question is further complicated by the presence of a relative as well as an absolute refractory period. But whatever the relation of the end of the refractory period to the decline of the state of excitation may be, it is probably a constant one\*; otherwise it is difficult to understand why the order of recovery should ever be the same as the order of excitation.

*Relation between T and the decline of the state of excitation.*

We have shown that the order of recovery of the various regions of ventricular muscle is the same as the order of excitation. Granted that the end of the refractory period is associated with the decline of the excitation process, then the formation of *T* and the decline of the excited state take place in part, if not wholly, during the same period. For the surface layers of the ventricular muscle, which are the latest muscle layers to become active, pass out of the refractory period before *T* is complete. The fact that the retreat of the excitation process occupies a much shorter interval than the formation of *T* is not antagonistic to the belief that *T* is the result of the decline of the state of excitation. The spread of the excitation process builds *Q.R.S.*, but the *Q.R.S.* interval is greater than the interval consumed in this spread by the time during which the last muscle region activated is developing its full negativity. By analogy, the interval during which *T* is written is equal to the time consumed in the retreat of the excitation process, plus the interval that separates beginning loss of negativity and complete loss of negativity in the muscle region that passes out of the excited state latest. Since the spread of the excitation process and its retreat occupy the same length of time, we must believe that the period of decreasing negativity is much longer than the period of increasing negativity. It is in this way that the long duration of *T* in comparison with the short duration of *Q.R.S.* is to be explained.

\* It is possible, of course, that this assumption may prove unwarranted.



It should be pointed out that in branch block curves and in many other curves *T* appears to begin before *Q.R.S.* is complete; it is often difficult to decide exactly where *Q.R.S.* ends and where *T* begins (Fig. 10). It is, therefore, hard to believe that, for the mammalian heart, there is any period during systole when the state of negativity is not changing in some part of the ventricular muscle; if there is any period when the electrical state of each muscle element is not changing, it must be a short one. It is undoubtedly true, however, that at certain times the state of negativity is changing more rapidly than at others: at the beginning of the active period the electrical state of muscle changes rapidly; subsequent changes in the electrical state probably take place more slowly. The curve *ABCD* of Fig. 3, in so far as it is intended to represent the electrical activity of mammalian heart muscle, should probably consist of but two portions, *AB* and *CD*.

*The effect of ethyl chloride.* The application of ethyl chloride to the ventricular surface modifies *T*; it also changes the order of recovery in the ventricular muscle. It is true, therefore, that *T* is modified by agents that disturb the decline of the excitation process. Is not the failure of ethyl chloride to affect *Q.R.S.* in conflict with this conclusion? If *Q.R.S.* and *T* are due to different phases of the same process, how is it that *T* may be modified by agents that do not modify *Q.R.S.*? The answer to this question probably lies in the nature of the excitation process. This process is evidently not a simple one, and there is no reason to believe that its end-phase may not be more easily modified than its initial phase. It should be remembered that although it is possible to change the form of *T* without changing the form of *Q.R.S.*, it is not possible to modify the latter without affecting the former.

*The T deflection in bundle branch block.* In right branch block *T* is positive. The surface of the left ventricle, the last part of this chamber to recover its excitability, passes out of the refractory state before or soon after the apex of *T* is written. The surface of the right ventricle does not recover until *T* is nearly complete. These facts suggest that the upstroke of *T* in right branch block is chiefly a left and the downstroke chiefly a right ventricular effect. A similar conclusion may be drawn from a study of the refractory period in left branch block; here also the downstroke of *T* seems to be chiefly a right and the upstroke chiefly a left ventricular effect. We say chiefly because the long duration of *T* as compared with the duration of *Q.R.S.* indicates that there must be a much greater overlapping of right and left ventricular effects in the formation of the former than in the formation of the latter. Furthermore, there is no part of the period during which *T* is written (except perhaps the last 0.05 or 0.06 second) when both ventricles are not in the excited state; and during the period of excitation the electrical state of the muscle of both chambers is probably changing (slowly or rapidly) continuously.

If the downstroke of  $T$  in left branch block is chiefly a right ventricular effect and the upstroke of  $T$  in right branch block is chiefly a left ventricular effect, then the curve obtained by the algebraic addition of these unilateral curves in the proper time relation should resemble  $T$  of the natural complex. An addition of this type has been performed in Fig. 2. It will be seen that the calculated curve resembles the normal  $T$  in general outline, especially in its early phases.

We may learn something further of the forces that combine to form  $T$  by a study of transitions of the type shown in Fig. 10. In the first part of this figure  $T$  becomes less negative with each succeeding complex. This change is associated with a decrease in the slope of the descending limb: the final limb does not change its slope but becomes shorter. What is the significance of the difference in behaviour of the two limbs of  $T$ ? The transition of this figure is produced by shifting the time relation of left and right ventricular effects. It will be seen that the change in the form of  $Q.R.S.$  that takes place from complex 4 to complex 6 (inclusive) is due to a change in the final portion of  $Q.R.S.$ : the first part of  $Q.R.S.$  ( $Q'$  and  $R'$ ) does not change. The explanation is simple: the first part of  $Q.R.S.$  is of unilateral origin, the last part of dual origin. It is quite evident that all parts of the ventricular complex which are not changed in form by shifting the relation of the true dextrocardiogram and the true levocardiogram are the expression of unilateral events: all parts that are changed are the expression of bilateral events. We conclude, therefore, that the first limb of  $T$  in complexes 1 and 2 is of dual origin: both right and left ventricular effects take part in its formation, although the right ventricular effects undoubtedly predominate: and that that part of the final limb of  $T$  which is identical in complexes 1 and 2 is of unilateral origin: it is the expression of left ventricular events. The duration of the upstroke of  $T$  in complex 1 is 0.074 second: in complex 2, 0.059 second: and in complex 3, 0.037 second. The upstroke in complex 1 is of too great duration, therefore, to be a pure left ventricular effect, but that part of it which appears unchanged in complex 2 may well be unilateral in origin.

It is generally true that slight changes in the relative positions of the levocardiogram and dextrocardiogram, when one of these curves precedes the other by a considerable interval, profoundly changes the shape of the first part of  $T$ , but does not change the shape of the last part. We believe that the last part of  $T$  (the part which occupies the last 0.04 to 0.06 second) in left branch block is a pure left ventricular effect and that the last part of  $T$  in right branch block is a pure right ventricular effect.

*Some factors that determine the form of  $T$  in combined complexes.*

Combinations of the levocardiogram and dextrocardiogram in different time relations show that the direction of the most prominent deflection of  $Q.R.S.$  is dependent upon two factors: (a) upon which of these two

curves precedes the other: the curve that precedes its fellow having the position of advantage: and (b) upon which of the two curves is of greater amplitude. When the precedence of one curve over the other is great, it is the deciding factor: when it is small, relative amplitude is the deciding factor. The same two factors can be distinguished in the formation of the *T* deflection: here, however, relative amplitude plays a greater rôle than in the formation of *Q, R, S*, for the slow development of the forces that build *T* tends to cause a fusion of all effects that are separated by small intervals of time. It is true that when the dextrocardiogram precedes the levocardiogram by a considerable interval, *T* is usually positive (Figs. 9 and 10): and that when the relation of these two curves is the reverse, *T* is usually negative: but when the interval by which one of these curves precedes the other is small, the direction of *T* is dependent upon which of the two ventricles produces effects of greater amplitude. When the right and left ventricles are stimulated, first separately and then simultaneously, the direction of *T* of the combination complex may be predicted: it has the same direction as *T* of the left ventricular extrasystole or as *T* of the right ventricular extrasystole according as the one or the other is of greater amplitude (Fig. 13).

It may seem strange that the thin-walled right ventricle can ever produce effects of greater amplitude than the more massive thick-walled left ventricle. It must be remembered, however, that the levocardiogram and the dextrocardiogram are resultants: not all of the forces that enter into the formation of either of these curves have the same direction: some are positive and some are negative. It is also probable that, because of the thicker wall of the left ventricle, the activation and deactivation of the muscle of this chamber are spread over a slightly longer period than the corresponding activities of the right ventricular muscle. Then there is the question of the lead used: some muscle regions are more advantageously situated with reference to the line of lead than other regions. And lastly, the expression relative amplitude, as used above, means relative amplitude in corresponding time-phases: as a rule the dextrocardiogram reaches its full amplitude earlier than the levocardiogram.

#### *Some theoretical considerations.*

It has been shown by Lewis<sup>3</sup> that the direction of the *Q, R* and *S* deflections is determined by the average direction in which the excitation wave is travelling when each is written. When the excitation wave is spreading from right to left, the right arm is negative with reference to the left arm and the deflection in lead *I* is upward. We may imagine that during this time each muscle element (strictly speaking the majority of the muscle elements involved) is relatively negative to its neighbour on the right and relatively positive to its neighbour on the left. As the

spread of the excitation wave nears completion we should expect all muscle elements to approach an isoelectric state: the galvanometer string should then return to the base line. When the excited state begins to pass off, following in its retreat the same path that it pursued in its advance, each muscle element should become relatively positive to its neighbour on the right and relatively negative to its neighbour on the left: the resulting deflection should be oppositely directed to the deflection produced by the spread of the excitation process. We should anticipate, therefore, that since the most prominent initial deflection of the true dextrocardiogram is positive its final deflection would be negative. For a similar reason, we should expect the final deflection of the true levocardiogram to be positive. The form of the ventricular complex in bundle branch block seems to support this hypothesis: when the chief initial deflection is positive  $T$  is negative and vice versa. We may conceive, therefore, that the true dextrocardiogram resembles curve  $D2$  of Fig. 5, and that the true levocardiogram resembles Curve  $L2$ .

There are, however, some objections to this hypothesis. If the true dextrocardiogram, after reaching its apex, returns at once to the base line, as indicated in Curve  $D2$ , how is it possible to explain the  $Q.R.S.$  of left bundle branch block? We have given evidence to show that the second peak of  $Q.R.S.$  in left branch block is  $R'$  of the levocardiogram superimposed upon the dextrocardiogram; this levocardiogram may differ from the normal levocardiogram, but we should expect it to have the same general outline. If we subtract the normal levocardiogram (its early phases) from the latter part of the  $Q.R.S.$  of left branch block, the dextrocardiogram is left well above the base line. It appears to descend sharply immediately after the first peak of  $Q.R.S.$ , but if this rapid descent continues it is difficult to understand why the downstroke of the levocardiogram does not carry the final limb of  $Q.R.S.$  far below the base line. We must believe, either that the early phases of the levocardiogram that enters into the formation of the left branch block complex are decidedly different from the early phases of the normal levocardiogram, or that the true dextrocardiogram does not descend to the zero line early.

If, now, we consider  $T$  and we conclude, for the reasons given above, that the last part of  $T$  in right branch block is a pure right ventricular effect, then the final phase of the levocardiogram, as well as its initial phases, appears to lie above the base line.

We may conceive, therefore, that the true dextrocardiogram resembles curve  $D1$  rather than curve  $D2$  in form, and that the true levocardiogram resembles curve  $L1$  rather than curve  $L2$ . These curves ( $D1$  and  $L1$ ) are purely hypothetical, and they are difficult to explain on theoretical grounds. The manner in which they are conceived to unite\* to form the complexes of right and left branch block is indicated by the broken curves in the

\* No attempt at accurate combination is made in the figure. It is intended to give a general idea, not an exact idea, of the way in which branch block complexes may be produced.



Fig. 5. The hypothetical form of the true levocardiogram ( $L_1$  and  $L_2$ ) and of the true dextrocardiogram ( $D_1$  and  $D_2$ ).

figure. In some respects they are no more satisfactory than the curves  $D_2$  and  $L_2$ .\*

We have entered upon this discussion of the form of the true levocardiogram and of the true dextrocardiogram in order that our statements in regard to  $T$  may not be misunderstood. In concluding, for instance, that

\* They (Curves  $L_1$  and  $D_1$ ) are unsatisfactory in several respects. If, in a single experiment, all the complexes obtained by stimulation of various regions of the surface of the right ventricle are compared, it is found that there is a relation between the amplitude of  $Q.R.S.$  and the amplitude of  $T$ . The taller  $Q.R.S.$  the more negative is  $T$ ; and when  $Q.R.S.$  is short,  $T$  may even be positive. If curve  $D_1$  represents the true form of the dextrocardiogram, this relation would not be anticipated. In the second place, Curves  $L_1$  and  $D_1$  indicate that in ventricular preponderance  $T$  should have the same direction as  $Q.R.S.$  This does not appear to be the case. It is true, however, that our knowledge of the effect of preponderance upon the electrocardiogram is limited, if we except the right ventricular preponderance that is present in the newly born infant, to the effect of preponderance in heart disease. But here the pure effects of preponderance are obscured by the effects of myocardial changes and variations in the position of the dilated heart.

the upstroke of  $T$  in right branch block is chiefly a left ventricular effect, we mean only that this part of  $T$  is due chiefly to the early decline of the excitation process in the left ventricular muscle. Whether it is an upstroke because of the average direction in which the excitation process is retreating during the time in which it is written, or because the deactivation of the left ventricular muscle disturbs a balance between right and left ventricular effects, we do not know. A positive  $T$  may be looked upon as the result of a preponderance of left ventricular effects (preponderant retreat of the excitation process on the left side), or as the result of a preponderance of right ventricular effects (preponderance of retained activity on the right side) according to the view taken. At present there does not seem to be more virtue in one view than in the other.

The effect of cooling various parts of the ventricular surface upon the  $T$  deflection may be expected to throw some light upon the problem, but it does not seem desirable to enter upon a discussion of this subject until more data have been accumulated.

*Relation of  $T$  to the final deflection of  $Q.R.S.$*  According to Lewis,<sup>1</sup>  $T$  of the toad's electrocardiogram is always opposite in direction to the final deflection of  $Q.R.S.$  : when there is an  $S$  deflection,  $T$  is positive ; when there is no  $S$ ,  $T$  is negative. It appeared to us at first that a similar relation was present in the majority of mammalian electrocardiograms. Further observation leads us to believe that, in mammals, the relation is fictitious. The apparent relation arises from the fact that, in many instances, the appearance of the end of  $Q.R.S.$  is determined by the direction of  $T$ . In left branch block, for instance, the final limb of  $Q.R.S.$  usually descends below the base line ; but since  $T$  is negative, no  $S$  is formed : a  $Q.R.S.$  of the same form followed by a positive  $T$  would show an  $S$  deflection. In the toad's electrocardiogram,  $Q.R.S.$  is followed by a long iso-electric or nearly iso-electric stretch of curve, and the relation between the direction of  $T$  and the final deflection of  $Q.R.S.$  is probably real. For this relation we have no explanation other than that offered by Lewis.<sup>4</sup>

### *Summary.*

1. Delayed conduction of the impulse through one of the chief branches of the His-bundle (incomplete bundle branch block) gives rise to ventricular complexes that are transitional in form between the normal complex and the complete bundle branch block complex. This conclusion is based upon :

(a) The form of the curves obtained by the algebraic addition of the levoecardiogram and dextroecardiogram in varying time relations.

(b) The form of the curves produced by the experimental combination of the levoecardiogram and dextroecardiogram in varying time relations.

(c) The form of the ventricular complexes recorded during the period of recovery that follows temporary bundle branch block.

2. Under normal conditions, the duration of the state of excitation is approximately uniform throughout the ventricular muscle. This conclusion is based upon :

(a) The order in which the various regions of the ventricular muscle pass out of the refractory state in bundle branch block.

(b) The order of recovery when the cardiac mechanism is normal.

(c) The relations that exist between the form of  $Q.R.S.$  and the form of  $T$  and between the length of the  $Q.R.S.$  interval and the length of the  $R-T$  interval.

3. The  $T$  deflection is produced by the decline of the state of excitation in the ventricular muscle. This statement is based upon :

(a) The relations between  $T$  and the end of the refractory period.

(b) The effect of cooling the ventricular surface upon the form of  $T$  and upon the refractory period.

(c) The relation between the form of  $T$  and the form of  $Q.R.S.$

4. In right branch block the beginning rise of  $T$  is chiefly a left ventricular effect ; the end of  $T$  is sustained by a right ventricular effect. In left branch block the beginning fall of  $T$  is chiefly a right ventricular effect ; while at the end it is sustained below the base line by left ventricular effects.  $T$  of the normal ventricular complex is a combination of right and left ventricular effects : the former tend to make  $T$  negative : the latter, positive.

NOTE.—We regret that Rothberger and Winterberg's study (*Zeitsch. f. d. ges. exper. Med.*, 1916-17, v. 264) did not come to our notice until after this article had passed into the hands of the publisher. They found that in many instances lesions of the bundle-subdivisions (especially lesions which divided the anterior or posterior limb of the left bundle branch) produced striking changes in the form of the ventricular complex but did not greatly change the  $Q.R.S.$  interval. The greatest change in the  $Q.R.S.$  interval observed amounted to 0.01 second.



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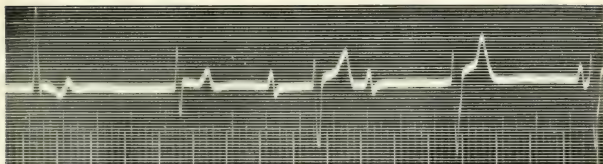


Fig. 6. Experiment 4. Lead *II*. Right branch block. The effect of right vagus stimulation. In this and the figures which follow 1 cm. equals approximately 1 millivolt. The time-marker records fifths of a second.

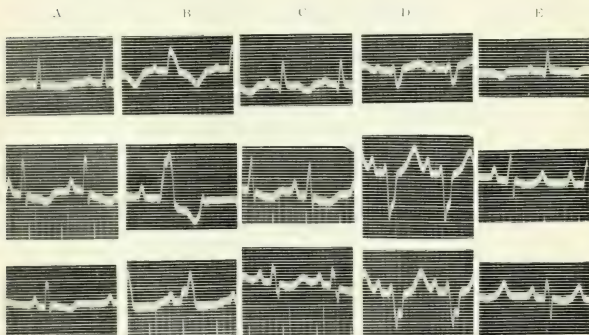


Fig. 7. Experiment 7. *A*—Control curves. *B*—Left branch block. *C*—Recovery. *D*—Right branch block. *E*—Recovery.

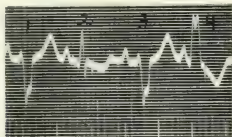


Fig. 8. Experiment 7. Lead *II*. Right branch block. Stimuli applied to right central region. Complex 4.—Right vent. extrasystole. Complex 3.—Right branch block complex. Complex 2.—Complex of normal type produced by superimposing the normal levocardiogram and the extrasystolic dextrocardiogram. Compare with the ventricular complex of the control curve (Fig. 7*A*, Lead *II*).



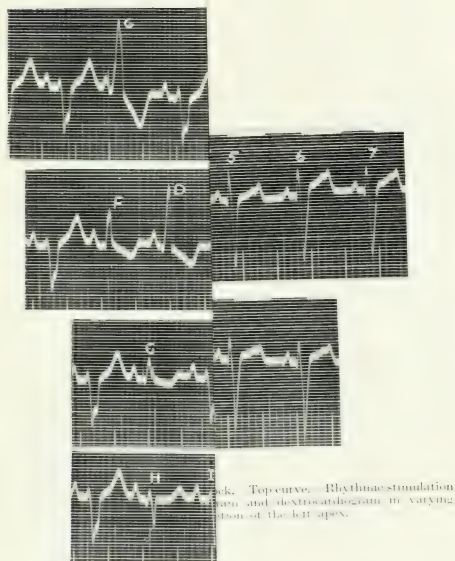


Fig. 9. Experiment 7. Lead II, Right Complex A.—Right vent. extrasystole, the levoecardiogram and dextroecardiogram

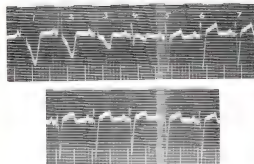
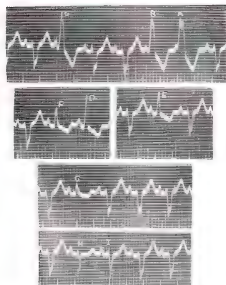


Figure 1. ECG strips showing cardiac rhythm.

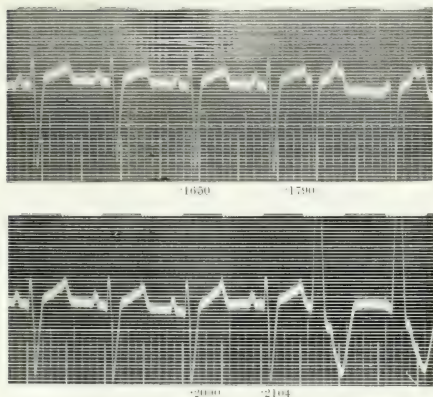


Fig. 11. Experiment 12. Lead *II*. Curve 1289. Top curve.—Rhythmic stimulation of right conus. The refractory period ended between 0.165 and 0.179 second after *Q*. Bottom curve.—Rhythmic stimulation of the left apex. The refractory period ended between 0.200 and 0.210 second after *Q*.

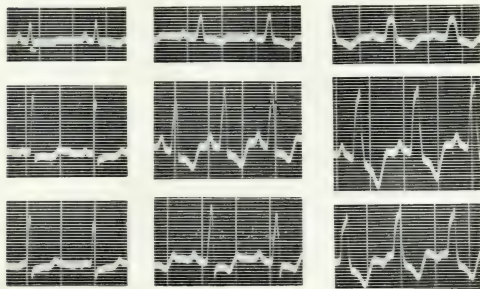


Fig. 12. Experiment 17. Left-hand curves.—Control curves in the three leads. Middle curves.—Incomplete left branch block. Right-hand curves.—Complete left branch block.



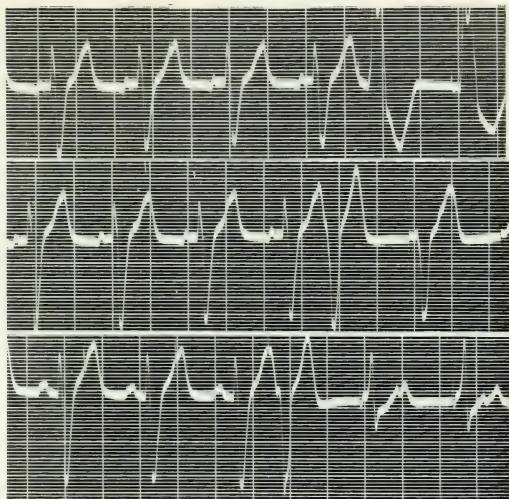


Fig. 13. Experiment 18. Lead *II*. Right branch block. Top curve.—Rhythmic stimulation of the right conus. Middle curve.—Rhythmic stimulation of the left apex. Bottom curve.—Simultaneous stimulation of conus and apex.

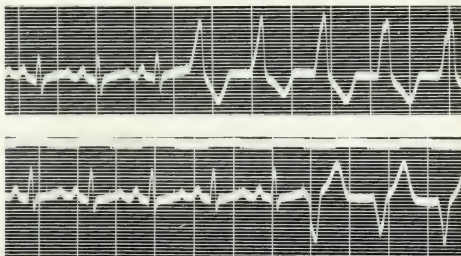


Fig. 14. Experiment 19. Normal mechanism. Top curve.—Rhythmic stimulation of the right central region. Refractory period ended between 0.122 and 0.141 second after *R*. Bottom curve.—Rhythmic stimulation of left apex. The refractory period ended between 0.146 and 0.151 second after *R*.





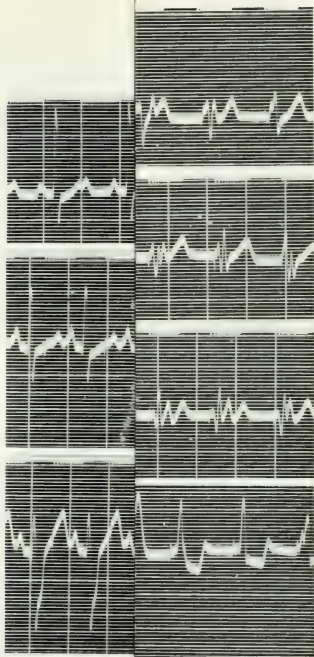
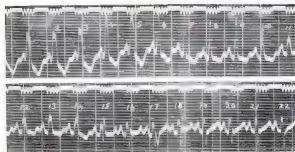
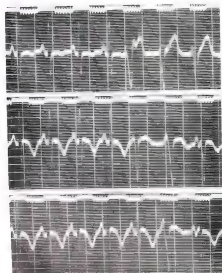


Fig. 15. Experiment 24. Top curve: Normal sinus rhythm. Simultaneous left-apex. Right central region blocked. The right central region recovered after *R*. Middle curve: Simultaneous after *R*. 2nd record, Lead *III*. Layers of the left apex. The deep, the right central region and the deeper stimulus fell 0.137 second after *R*. Apex recovered first. Earliest effective layers of the right central region and *III*. Left region blocked. Simultaneous right side struck and injured the apex. Right central region recovered block. Earliest effective stimulus fell. Simultaneous stimulation of the injured first.



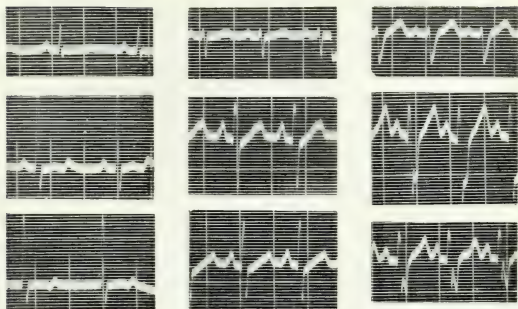


Fig. 17. Experiment 21. Left hand records.—Control curves. Middle records.—Incomplete right branch block. Right-hand records.—Complete right branch block.

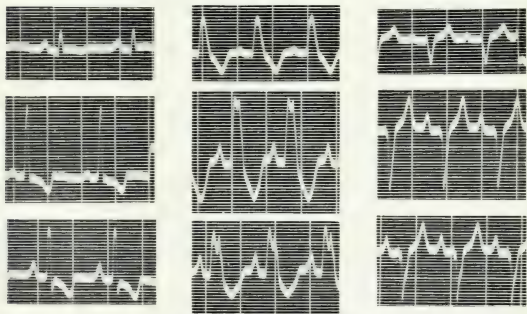


Fig. 18. Experiment 22. Left-hand records.—Control curves. Middle records.—Complete left branch block. Right-hand records.—Complete right branch block.



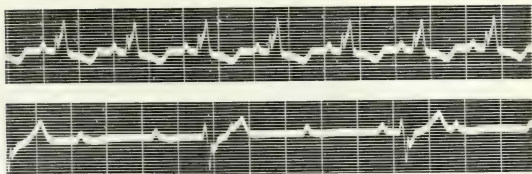


Fig. 19. Experiment 19. Lead II. Top curve—Left branch block. Bottom curve—Bilateral branch block.

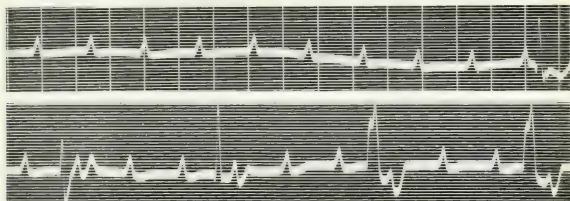


Fig. 20. Experiment 22. Bilateral branch block immediately after second cut. Top curve—Ventricular standstill following second cut. Bottom curve—Simultaneous activity of two ventricular pacemakers.

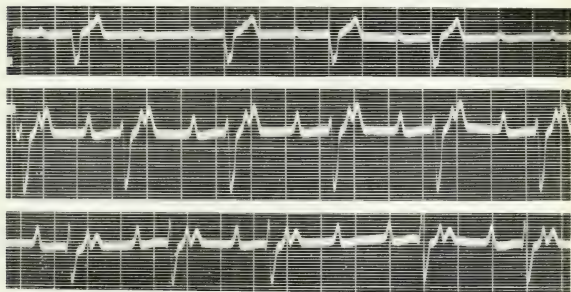


Fig. 21. Experiment 22. Beginning recovery of the left branch of the bundle. Complete right branch block and incomplete left branch block.



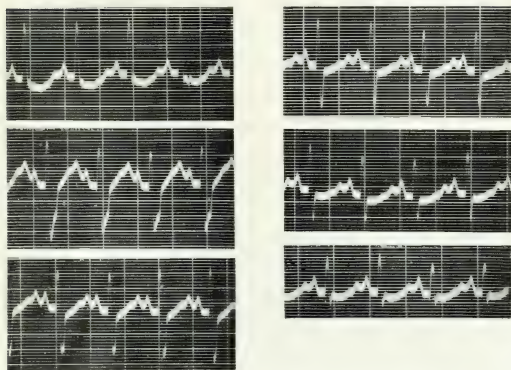


Fig. 22. Experiment 24. I.—Control curve. II.—Right branch block. III, IV, and V.—Incomplete right branch block. VI.—Recovery.

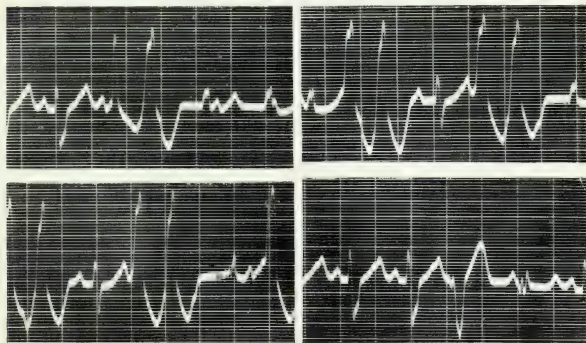


Fig. 23. Experiment 24. Simultaneous stimulation of right central region and left apex. Make shock interpolated in the middle of every second inter-beat shock interval. 1, 2 and 3.—Strong stimuli. 4.—(Lower right-hand curve) Strength of stimuli reduced until make shock was below threshold value.





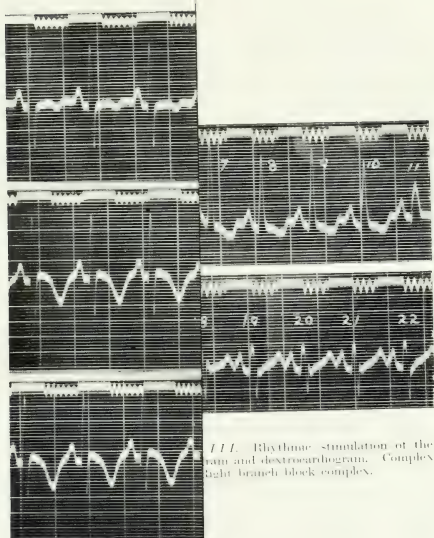


FIG. 24. Rhythmic stimulation of the ram and electrocardiogram. Complex right branch block complex.

Fig. 24. Experiment 26. Top curve.—Rho stimulus fell 0.167 second after *R*. Mid the left apex after spraying the left apex 0.231 second after *R*.



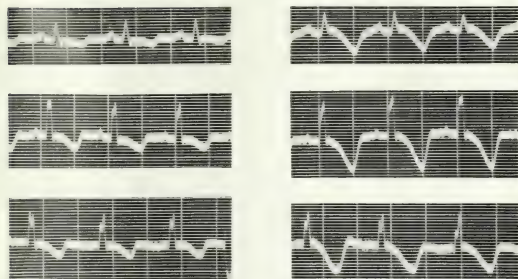


Fig. 26. Experiment 32. Left-hand records. Control curves. Right-hand records. After 1 mg. of morphine. After 1 mg. of atropine. (Note the marked bundle branch block in the right-hand records.)

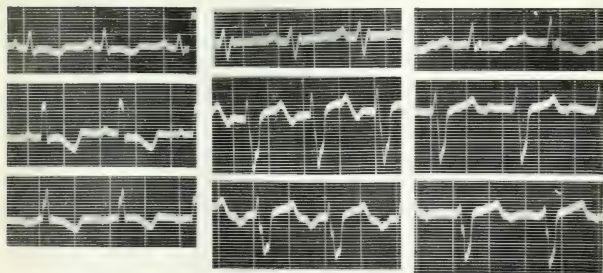


Fig. 27. Experiment 32. Left-hand records. Control curves. Morphine records. Right-hand records. After cutting the anterior limb of the left branch.



## REPORT OF A CASE OF CONGENITAL ANOMALY OF THE HEART—REPTILIAN.

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Medical School, Portland, Oregon.)*

THE more common anomalies of the heart, namely, patent foramen ovale and patent ductus arteriosus, occur too frequently to be of unusual interest. Other less common errors in formation are as a rule sufficiently unique to warrant recording.

On July the 12th, 1920, a white male baby of Austrian parentage was born at the Good Samaritan Hospital. It was seen by one of us (C. U. Moore), in consultation with Drs. Dalton and Shoot, when five days old. It was the fourth child of healthy parents. The three other children were instrumental deliveries, and are normal and healthy. There had been no miscarriages. The babe was delivered at full term by Caesarian section. It took the breast well for the first three days, then refused it. Physical examination showed a well developed, well nourished white child weighing six pounds. Cyanosis was marked. The lips, gums, buccal mucous membranes, eyelids, fingers and toes were a deep purple. The colour was less deep in other parts. Cyanosis was more extreme during crying. Feet and hands were cold. Rectal temperature was normal. The head was well formed, the anterior fontanelle was 2 by 3 cm., eyes, ears, and nose were normal, the throat was clear. There were no glandular enlargements. The chest was well formed: over the lungs moist râles of general distribution were heard. The cardiac dullness extended 2 cm. to the right and 6 cm. to the left of the median line. A murmur replacing the normal sounds heard at the apex was audible over the entire cardiac area. There was no second sound, but the murmurs heard were separated by a short diastole. The abdomen was level; the liver was 3 cm. below the costal margin in the mammary line; the navel was healing normally. The genitals and rectum were normal. The extremities were symmetrical and normal. The reflexes were not elicited. Death occurred on the following day, and the autopsy revealed the cause of the cyanosis and the short duration of life.

The salient pathological findings are as follows : congenital malformation of the heart : absence of interventricular septum : absence of left atrio-ventricular opening : small aplastic left auricle : widely patent foramen ovale : acutely dilated heart : marked edema and hyperæmia of the lungs ; acute generalised passive hyperæmia ; absence of other malformations or malpositions of viscera : absence of any other disease process adequate to explain the cause of death.

Peacock and others reported a number of instances of septal defects, but a careful search of post writings for the past twenty years has failed to disclose a report of a case exactly similar to the one here reported.

In order to more clearly understand the conditions of the heart we are about to describe, it seems advisable to briefly review the pertinent features of its customary or normal development.

The embryo of 5 to 6 mm. in length contains a heart in which the form of the atria is more or less definite. There is also seen a slight indentation at the lower margin. This marks the formation of the apex and lies over the site of the future interventricular septum. A single vessel, the bulbus cordis, leads out of the single ventricle (see Fig. 1). The septa are not yet developed.

Later, in about a 12 mm. embryo, definite changes in the interior of the heart are noted. The endocardial cushions have united and have become fused with the septum primum to the end that the atrio-ventricular openings are formed and the foramen ovale is in evidence. The interventricular septum has not yet developed, and the single ventricle persists (see Fig. 2).

In the later stages of growth the bulbus cordis is divided in a twisting plane so as to form two vessels, the pulmonary artery and the aorta, which maintain communications with the right and the left ventricles respectively, the ventricles having been divided by the interventricular septum (see Fig. 3). The atrio-ventricular openings are complete and guarded by the tricuspid and mitral valves. The foramen ovale and ductus arteriosus are almost obliterated.

With the above sketch of the normal development of the heart in mind, let us consider the conditions that obtain in the instance here reported (see Fig. 4).

The heart, opened after fixation, weighs 26.5 gm.. The ventricular portion measures 4 by 4.5 cm. in its various dimensions. The epicardium presents no noteworthy changes. From the anterior presenting surface the coronary vessels extend obliquely from right to left. They appear to issue from the auriculo-ventricular groove immediately beneath the right auricular appendage. From here they extend down to the left in the direction of the apex of the heart. Their course and manner of distribution point to their being branches of the posterior artery. When the anterior surface of the heart is opened in the direction of what appears to be the pulmonary artery

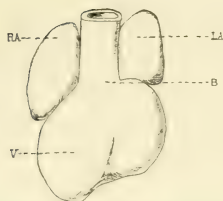


Fig. 1. Diagrammatic sketch of the heart, illustrating the second stage of development of the heart as it occurs in a 6 mm. embryo. *LA*=left atrium; *RA*=right atrium; *V*=single ventricle; *B*=bulbus.

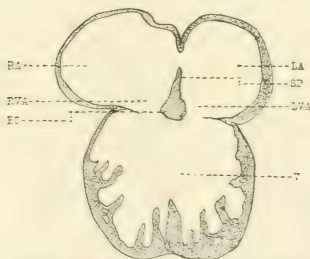


Fig. 2. Diagrammatic sketch of the internal structure of the heart chambers in the third stage of development. *LA*=left atrium; *RA*=right atrium; *SP*=septum primum; *EC*=endocardial cushion; *RAV*=right auriculo-ventricular opening; *LAV*=left auriculo-ventricular opening; *V*=single ventricle.

only a single ventricle is found. The large, and only, vessel leaving it is guarded by a tricuspid valve without evidence of the mouths of the coronary arteries. Some 0.8 cm. above the attachment of the cusps, the right and left branches of the pulmonary artery are given off. Immediately below the mouths of these vessels the artery has a circumference of 2 cm., which is also the circumference of the thoracic portion of the systemic aorta with which it is continuous. One cm. and a half above the branches of the pulmonary artery there is an opening guarded by a spur-like ridge, as is commonly found at the normal site of the isthmus of the aorta, where the ductus arteriosus normally enters it. The vessel entering here is apparently that portion of the arch of an aplastic systemic aorta. From the curvature of the latter the right innominate artery and its branches, the left common carotid, and the left subclavian, take their origin. This vessel, which has a circumference of less than a centimetre, arises at a point between the auricles and behind the beginning of the pulmonary artery. When it is opened it is found to end blindly, and has at its beginning small atypical cusps with pit-like depressions from which the mouths of the coronary arteries arise. There is no connection between this vessel and the single ventricular chamber. The right auricle is about three times the size of the left. The pulmonary veins enter into the latter, which is capable of holding about 3 cc. of blood. There is no opening between it and the ventricle. There is present a relatively large patent foramen ovale in the inter-auricular septum, which is otherwise complete in its development. The superior and inferior venæ cavæ enter normally, the latter being guarded by a narrow membranous Eustachian valve. The coronary sinus opens posteriorly, and at its opening there is a fenestrated membranous valve-like structure. The right atrio-ventricular orifice is 6.0 cm. in circumference and is guarded by a tricuspid valve. The greatest diameter of the ventricular chamber is 3 cm. In the vicinity of the apex there is a small prominence, which is probably the site of the undeveloped interventricular septum. In the upper portion of the ventricle there is found a single minute chorda tendina. It is on the left wall, and its upper attachment ends at the blind portion where the mitral valve should be found.

The characteristics of the circulation are as follows: The blood from the superior and inferior venæ cavæ, and that from the pulmonary veins (via the foramen ovale) enters the right auricle. From here it passes through the tricuspid valve into the single ventricle. From the ventricle it is pumped into the large pulmonary artery, a part of it entering the right and left branches and the remainder continuing on through the greatly dilated ductus arteriosus to the point where it normally joins the systemic aorta. Here the stream again divides, part continuing down the thoracic aorta, and the other portion turning to the left enters the arch and the mouths of the vessels leaving it, and in a retrograde manner returns to the heart musculature through the small aplastic aorta and the coronary arteries.



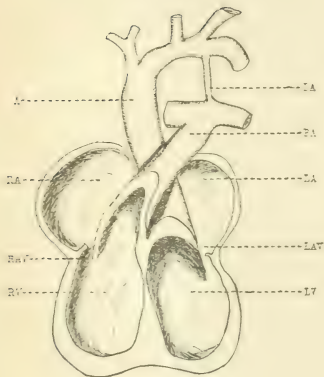


Fig. 3.

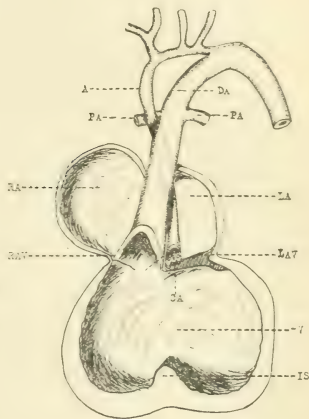


Fig. 4.

Fig. 3. Diagrammatic sketch of the heart in the final stage of development, illustrating the method of formation of the pulmonary artery and the systemic aorta from the bulbus cordis and the connection of these vessels to the right and left ventricle respectively, the interventricular septum being complete. *RA*=right atrium; *LA*=left atrium; *LAV*=left auriculo-ventricular opening; *RAV*=right auriculo-ventricular opening; *RV*=right ventricle; *LV*=left ventricle; *PA*=pulmonary artery; *A*=aorta; *DA*=ductus arteriosus.

Fig. 4. (Heart 5791.) Sketch illustrating the character of the deviation from normal in the heart reported. *RA*=right atrium; *LA*=small aplastic atrium; *LAV*=left obliterated auriculo-ventricular opening; *RAV*=right auriculo-ventricular opening; *V*=single ventricle; *IS*=anlage of interventricular septum; *PA*=pulmonary artery; *A*=aplastic aorta; *DA*=enlarged ductus arteriosus; *CA*=small openings of the coronary arteries.

The atypical character of the heart in question is undoubtedly the result of the closure of the left atrio-ventricular opening by too complete a fusion of the endocardial cushions on this side of the heart, together with the failure of development of the interventricular septum. There is established as a result of this imperfection a reptilian central circulation with universal distribution of partially venous blood. This type of heart is extremely rare and is incompatible with human existence.

THE VALUE OF VAGAL STIMULATION IN PAROXYSMAL  
AURICULAR TACHYCARDIA AS ILLUSTRATED IN AN  
UNUSUAL CASE.

By Dr. D. C. WILSON.

(From the Medical Clinic of the Peter Bent Brigham Hospital, Boston, Mass.,  
U. S. A.)

It is generally agreed that paroxysmal auricular tachycardia is the assumption by the heart of a regular rapid rhythm during which the auricle and ventricle contract at the same rate. The new rhythm usually begins and ends suddenly. It frequently is ended by stimulation of the vagi and is not influenced by digitalis in contradistinction to an allied condition, auricular flutter. That paroxysmal tachycardia seldom causes a cardiac rate greater than 200 to 225 is also true. The condition is not usually accompanied by a severe symptomatology or followed by serious or permanent damage. Tightness in the chest, shortness of breath and cardiac palpitation are the customary complaints. If the attack is prolonged the patient suffers more severely. The prognosis, however, is rarely considered grave, and the condition is allowed to continue in the majority of cases to stop spontaneously.

The purpose of presenting this case is to illustrate the possible emergencies that may accompany an attack of paroxysmal tachycardia, and the benefit which may result when the attacks are aborted. This patient suffered so unusually and was so seriously crippled by his seizures that it was imperative to stop them immediately.

Case No. 2,092.

H. W. R., a white man of 38 years, is a baker. He entered the Peter Bent Brigham Hospital on the 28th of December, 1914, complaining of a rapid heart.

*Family history.* His father died of shock at 65 years of age. One sister died of tuberculosis. One child is living and well, one died at birth. His wife is healthy and has had no miscarriages.

*Habits.* The man takes no alcohol and uses no tobacco.

*Past history.* At 14 years of age he suffered from mumps and pneumonia ; he had measles at 23 with tonsilitis, and neuralgia over his right eye at 29. He has never suffered from rheumatic fever or chorea, and denies having suffered from venereal disease. He states that he has had no cardiac symptoms before present illness.

*Present illness.*

*First attack.* The patient's heart beat rapidly for the first time in 1911 and his symptoms were similar to those on admission. The attack lasted five days. It was followed by blurred vision, diplopia of five weeks' duration, and loss of memory, which cleared up after a year.

*Second attack.* In 1912 his heart suddenly assumed a rapid rate. The paroxysm lasted eight-and-a-half days. He was seen by Dr. E. P. Joslin and Dr. Van Norden at the Boston City Hospital. In the sixth and seventh days of the attack a right hemiplegia developed without loss of consciousness. The paralysis cleared up in six months, leaving him with right sided weakness.

*Third attack.* This paroxysm began on March the 12th, 1913, and continued until March the 22nd. On the 20th of March the patient developed pains in his left forearm. The arm soon became pulseless, discoloured, and evidently gangrenous. On March the 26th it was amputated just below the shoulder for "dry gangrene."

*Fourth attack.* The patient was first seen by us at the Peter Bent Brigham Hospital on December the 28th, 1914. On December the 26th, 1914, he fell down stairs, but noted nothing unusual until the morning of December the 27th. His heart then began to beat irregularly, and soon became rapid in its action with occasional irregular periods. During these irregular periods he felt dizzy and had pain over the heart, a symptom he had not previously experienced. On his entry into hospital on December the 28th he was short of breath, felt weak, but there was no cough or orthopnea.

*Physical examination.*

He was a well developed and nourished man lying in bed ; his expression was anxious. The respiratory rate was increased slightly, but breathing was not laboured ; the skin was covered with profuse perspiration. The heart's impulse was seen and felt in the 5th space in the nipple line, 12 cm. to the left of the middle line : the left border of dulness by percussion corresponded ; the right border of dulness lay 3 cm. to the right of the middle line. On auscultation a regular rapid rhythm of 250 to the minute was counted, this rate being confirmed electrocardiographically (Fig. 1). No murmurs

were audible: the first and second sounds were distinct at the base, but only one sound was to be heard at the apex. The peripheral vessels seemed normal to palpation; the systolic blood pressure was 94 and the diastolic 86. There were no signs in the lungs. The left arm was missing below the shoulder. There was no oedema nor cyanosis. The knee jerks were more active on the right than on the left.

*Further examination and course.*

The Wassermann reaction proves negative. The stools and urine are normal. On December the 29th (during the attack) the leucocytes numbered 21,300; the hæmoglobin percentage was 111. Differential cell count:—Polymorphonuclears 80 per cent., small mononuclears 15 per cent., large mononuclears 4 per cent., basophiles 1 per cent. On December the 31st (after the attack) the leucocytes numbered 7,700. The temperature during the attack was 101 degrees F., after the attack it fell to 98.6 degrees F. On December the 29th vagal and ocular pressure were without effect. On December the 31st the rate fell suddenly to 110 and the heart was regular. On January the 1st the systolic blood pressure was 100, and the diastolic 66. On January the 5th the systolic blood pressure was 114, and the diastolic 84. Measurements of the heart by X-ray showed a transverse diameter during the attacks of 14.4 cm., and after the attack a transverse diameter of 11.9 cm., a diminution of 2.5 cm. (Fig. 2). The patient was discharged on January the 5th in good condition.

*Fifth attack.* On July the 14th, 1915, his heart seemed to stop and then resumed its beating at a rapid rate. The patient immediately came to the hospital. His physical examination gave similar signs to those found at his previous admission. The systolic blood pressure was 84, and the diastolic 76. The cardiac rate counted with the stethoscope and electrocardiographically was 235 to the minute. The attack was stopped by right vagal compression. The cardiac rate fell to 112. On July the 15th the systolic blood pressure was 130, and the diastolic 90; the cardiac rate had fallen to 90. The patient was taught how to stimulate his own vagi and was discharged. He again returned on July the 3rd, 1918, in another attack, the first for several months. He had previously experienced, however, several attacks which he had controlled by pressing on his carotid artery. The tachycardia was interrupted at this admission by the holding of a deep inspiration. Electrocardiograms of the transition showed auricular tachycardia of 212.77 changing into a ventricular tachycardia of 229.01. The latter was followed by the normal rhythm with frequent auricular extrasystoles. The patient wrote in December, 1919, that he was suffering from generalised epileptiform convulsions. He had experienced only two heart attacks, both of which he had controlled. When last heard from, the patient stated that the epileptiform attacks had ceased, and that he could prevent his heart from assuming a rapid rate by using vagal pressure when he felt the prodromal symptoms.

*Discussion.*

The rapid ventricular rate of 250 shown in this case is very unusual. The fact that auricular flutter frequency has a slower auricular rate than 250 emphasises the point that it is not the rate itself but the type of mechanism which differentiates the two conditions. Although the heart was contracting very rapidly it was possible for three independent observers to count the rate accurately with an error of two beats. A further point of interest, which may throw light on the cause of the gangrene, the amnesia and the hemiplegia, is the observation that the systolic pressure and pulse pressure were always very low during the tachycardia. The difference between the diastolic and systolic pressures during several attacks was but 8 mm. Hg, while during the normal rhythm it was 30 mm. or more. The unusual leucocyte count and the rise in temperature during a paroxysm are also interesting. Fig. 2 shows the size of the heart during and after an attack. The dilatation here is unusual, as X-ray examinations of similar attacks in other patients often fail to show any material enlargement. The increase in diameter in this instance was probably due to the extraordinary rate and to the weakness of the heart muscle as evidenced by a striking pulsus alternans observed in both brachioigrams and electrocardiograms.

The outstanding feature of the case, however, is the emphasis it places on the value of vagal stimulation. When an attack of paroxysmal tachycardia begins it is impossible to predict when it will stop. The possible disastrous results that may ensue make it imperative to end the attack if it is possible. Particularly is this true, if there is poor peripheral circulation as shown by a low pulse pressure. The chief methods of stimulating the vagi which are available to the patient are direct vagal compression, ocular compression and deep respiration. Occasionally, nevertheless, the attack is not influenced by any of the above procedures until they have been repeated again and again. Sometimes the paroxysms defy all such treatment.

## SUMMARY.

A case of paroxysmal tachycardia is presented, in which the heart dilated 2.5 cm. during the attack. Aphasia, hemiplegia, gangrene of one arm occurred during attacks of tachycardia. Epileptiform convulsions later developed, which were probably due to cerebral changes caused by the previous paroxysms. Observations on the pulse pressure were made. This was found extremely small, and is considered responsible for the complications from which the patient suffered. After the patient had been taught to control his attacks by vagal stimulation (direct pressure over the carotids, ocular pressure, deep breathing, etc.) they ceased to be a menace.

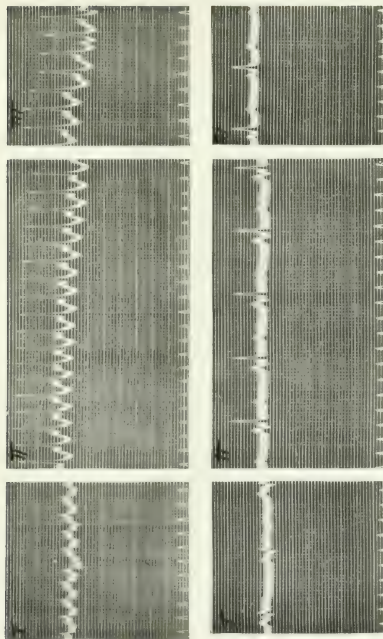


Fig. 1.

The upper tracings are the electrocardiograms showing the three customary leads taken during the tachycardia. The rate is 251 per minute. The lower tracings are the electrocardiograms after the attack, and show normal rhythm. The rate is 73.





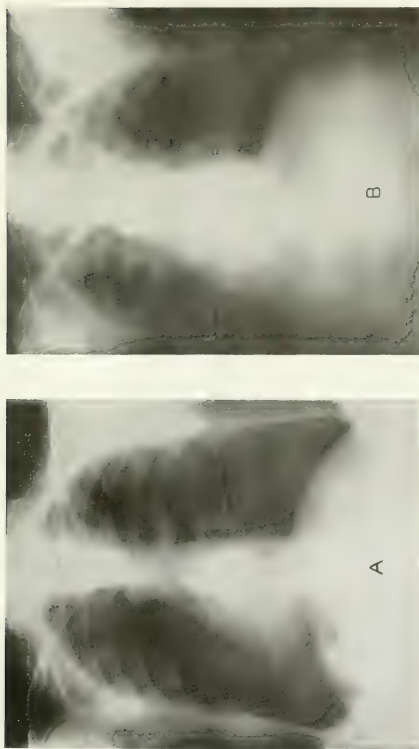


Fig. 2. A Radiogram of the heart 12 hours after an attack. B Radiogram of the heart during an attack, showing enlargement of 2.5 cm.; note that the enlargement is more marked to the right.



## FURTHER OBSERVATIONS UPON THE STATE OF RAPID RE-EXCITATION OF THE AURICLES.

By THOMAS LEWIS, A. N. DRURY and C. C. ILIESCU.\*

### *Methods of producing the state of rapid re-excitation.*

It is known that vagal stimulation will often throw a fluttering auricle, and will usually throw a fibrillating auricle, into a state of rapid re-excitation,<sup>1</sup> this reaction is due to the influence of the vagus upon the refractory period of the auricular muscle. The refractory period under vagal stimulation becomes greatly reduced<sup>2</sup> and the auricle becomes capable of responding to very rapid impulses. This reaction has been described fully in a previous communication.<sup>1</sup> It has been shown also<sup>2</sup> that a similar state is produced locally in the auricle, as a result of simple faradisation: in this instance the faradic current directly stimulates the vagal nerve endings and brings the muscle of this area into a condition in which it is capable of responding to the frequent shocks of the faradic stimuli. The state is confined in the last circumstance to a small area, because the region over which the vagal endings are stimulated is a limited one and the refractory period of the auricular muscle is not universally affected.

Rapid re-excitation of the whole auricle occurs in a variety of circumstances: it is not a reaction peculiar to the fluttering and fibrillating auricle.

Thus, it may appear when the auricles are responding to rhythmic shocks and the vagi are stimulated; such a reaction is by no means invariable, but it becomes more frequent as the rate of rhythmic stimulation is advanced. It is rarely seen when the rate of stimulation is less than 300 or 400 per minute, *i.e.*, at rates somewhat lower than those which usually prevail in flutter in the dog's auricle. On the other hand, the reaction is invariable when rates equivalent to those commonly termed "faradic" are employed, *i.e.*, 2,500 to 3,000 per minute. If the auricles are beating in response to rhythmic stimulation at a rate of about 400 per minute, the vagi may be repeatedly stimulated without the reaction appearing: now and again, however, the state of rapid re-excitation is produced. An example

\* Working on behalf of the Medical Research Council. The experiments here reported have been performed on dogs, all fully anaesthetised with morphia, paraldehyde and ether, throughout the experiments.

is shown in Fig. 4. In this the auricle is responding to rhythmic shocks at a rate of 420 per minute and has been under the influence of strong right vagal stimulation for about 10 seconds: the reaction occurs abruptly. It does not usually occur when the vagal influence is at its height; thus, in some animals it will happen repeatedly as the auricle is passing under the influence of the vagus, or as it begins to recover from this influence. There appears to be a critical point, *i.e.*, the state of rapid re-excitation would seem to appear when the refractory period has been reduced to a particular level, a level suited to the rate at which the auricle is responding rhythmically. That this critical relation exists is demonstrated most clearly by the dependence of the reaction upon the order of stimulation. Some auricles, responding rhythmically to stimulation at rates of 400 per minute (most auricles responding at rates of 600 per minute), will invariably break into the state of rapid re-excitation when the vagus is stimulated; but if in these the vagi are first stimulated and the rhythmic shocks are not applied until the auricle is fully under the vagal influence, the reaction is not seen, the auricle continuing to respond regularly to the rhythmic shocks: in such circumstances the refractory period has been reduced below the critical point before the rhythmic shocks enter it.

Very rarely, the normally beating auricle is thrown into the state of rapid re-excitation by vagal stimulation. Thus, in one animal, though only for a short phase of the experiment, this reaction was seen repeatedly, and is portrayed in Fig. 5. Three normal beats (*a, b, c*) of the auricle are shown in direct leads from the base and tip of the right auricular appendix. Vagal stimulation begins shortly after the first of these beats. The first change is the usual profound slowing of the auricle, but the third beat (*c*) is at once followed by the state of rapid re-excitation. The meaning of this very occasional reaction is not clear; being extremely rare it becomes very difficult further to investigate. It is probable that in auricles which display it the muscle is in an exceptional state. With this seeming exception, there is a very clear relation to the preliminary rate of beating. It is natural to imagine that the relation may depend upon the interval separating succeeding stimuli, an idea which is readily put to the test and confirmed.

If under vagal stimulation the auricle is stimulated rhythmically at rates of about 200 per minute and occasional make and break shocks are also sent into the same point, the latter will fall at varying relations to the rhythmic shocks. When an occasional shock falls within a certain distance of a rhythmic shock, the state of rapid re-excitation is set up invariably. Our observations are given in Table I.

These readings are taken from our experiments upon the refractory period of the heart under vagal stimulation:<sup>3</sup> each reading of the table is the interval in seconds which separates a testing shock from the last of two effective rhythmic shocks. The table includes readings of only those testing shocks which yielded responses, and such readings are arranged according to the type of reaction. To take an example from the present table, in

TABLE I.

*Response to single shocks interrupting rhythmic stimulation of auricle during vagal stimulation.*

Dog	..	..	LP.	LQ.	LR.	LS.	LZ.	MH.
Rate of Stimulation			235	220	204	208	180	205
Single Response						0.161m		0.149b
						0.160m		0.140b
						0.136b	0.176m	0.126b
						0.134b	0.169b	0.117b
						0.126m	0.163m	0.115b
						0.115m	0.147m	0.113b
			0.146m	0.138b	0.189m	0.102m	0.146m	0.092b
			0.144m	0.108m	0.134m	0.102m	0.123m	0.091b
			0.135m	0.097b	0.099m	0.094b	0.113m	0.088b
			0.128m	0.093m	0.093m	0.083m	0.086b	0.084b
Double Response			0.088b			0.096m	0.077m	0.076b
							0.073b	0.073b
							0.071b	0.071b
			0.069m		0.041b		0.059m	0.059m
Rapid re-excitation*			0.068m	0.084m&b	0.071m	0.063b	0.039b	0.065b
			0.067m	0.083m	0.069m	0.052b	0.041b	0.062b
			0.062m	0.062b		0.040b	0.036m	0.057b
			0.054b	0.058b	0.047m		0.031m	0.040b
			0.051b	0.048b		0.033m	0.029b	0.039b
			0.051b	0.046m	0.043m	0.033b	0.025b	0.036b
			0.048b	0.045b		0.033b	0.018b	0.034b
			0.048m	0.042m	0.029m	0.030b	0.016b	0.029b
Absolute refractory period			0.037m	0.038m	0.020b	0.025b		0.028b
			0.036	0.030	0.020	0.024	0.014	0.028

\* In a few instances, the auricle failed to respond when the reading approached that of the absolute refractory period. This occurred in the case of dogs *LQ*, *LS* and *MH* (see Table I of our previous article (?)).

† m = response to make and b = response to break shock.

dog *LP* the absolute refractory period measured 0.036 of a second under vagal stimulation (see Table I of the previous communication<sup>2</sup>). All testing shocks falling from 0.036 to 0.068 of a second after the last rhythmic shock gave, not a single, but a multiple response (rapid re-excitation). All testing shocks falling outside these limits failed to yield a multiple response. Falling at 0.069 and at 0.088 of a second, the response was double, falling at 0.128 of a second and over, the response was invariably single. The remaining experiments of the table display similar reactions. The time reading for the last multiple response is relatively consistent, lying as it does between 0.059 and 0.084 of a second; it averages 0.069 of a second. When the dog's auricle is fully under vagal stimulation, and is responding regularly to

rhythmic shocks at rates averaging about 200 per minute, the cycle (length 0.3 of a second) is divisible into three periods. There is a period of absolute refractoriness, having an average duration of 0.025 of a second: there is a period, immediately beyond this, which averages about 0.044 of a second in length (up to 0.069 of a second) during which a single shock creates a multiple response. From 0.069 of a second to the end of the cycle, *i.e.*, a period of 0.231 of a second, a single shock yields with few exceptions a single response. The exceptions, a pair of beats constituting a double response,\* are not always seen: they lie usually, as the table shows, in an intermediate zone, between that of single and multiple responses. In some instances (readings 0.044 and 0.050) these double responses fall in the zone in which multiple response is anticipated, in one instance (reading 0.096) in the zone in which a single response is anticipated: otherwise their arrangement is orderly. More important is the sharpness with which the reaction by multiple response ends. The multiple response is invariable when the interval stands at 0.06 of a second or less: an interval of this length exists between the beats when the auricle is responding to rhythmic shocks at a rate of 1,000 per minute. We should expect to find that if the auricle is first brought fully under vagal control and then stimulated rhythmically at this rate or at higher rates, that the setting up of rapid re-excitation would be invariable. This, as we shall see, actually proves to be the case.

A parallel reaction† to those last described has been recorded by Mines,<sup>5</sup> who worked with the cooled and perfused rabbit's ventricle beating in response to natural impulses. Mines showed that if single shocks were sent into the ventricle beating under these conditions, a *properly timed* stimulus immediately sets up a continuous and rapid action of the ventricles. His remarks, and the figures which illustrate them, indicate that the shock must enter at a critical instant (or during a very short critical period), namely, immediately at the close of the refractory period. He states that if the shock falls later it merely induces an extrasystole: this is not precisely true, for his own figures clearly show that there is a short period during which a single shock gives two responses. Very similar reactions have been repeated in much detail by de Boer,<sup>1</sup> who worked with the anæmic frog's ventricle. In these experiments of Mines and de Boer the muscle is responding rhythmically, and an extra-stimulus falls prematurely upon it and provokes the state of rapid re-excitation. In our experiments, is the reaction dependent upon a series of rhythmic shocks being followed by a premature shock, or are the last two shocks of the series if properly coupled sufficient to produce it? This question has been tested by using a long pendulum, which, in its swing, knocks over a pair of break keys. The keys may be set at appropriate and graduated distances from each other, and thus two break shocks are thrown into the muscle at an interval which may be varied at will. The

\* The response is by 1, 2 or very many beats. We have never seen 3 or 4 responses.

† Though the heart was not under vagal stimulation.

TABLE II.

*Response of auricle to two shocks during vagal stimulation. (Shocks apart in seconds.)*

Dog .. ..	M L.	M M.	M N.	M O.
Single response to second shock.	0-168	0-105	0-163	0-158 (4)
	0-123	0-098	0-163	0-150 (2)
	0-114	0-098	0-153	0-142
	0-114*	0-098	0-153	0-142
	0-110*	0-095	0-145	0-133
	0-106*	0-091	0-139 (2)	0-118
Variable response to second shock.	0-094 D.R.	0-090 R.Re	0-139	0-110
	0-091 S.R.	0-090(2) D.R.	0-130(2) R.Re	0-110 D.R.
	0-086 D.R.	0-090 R.Re	0-130 S.R.	0-110 S.R.
	0-079 R.Re	0-086(2) R.Re	0-125(2) D.R.	0-103 S.R.
	0-077 (2) D.R.†	0-086(2) S.R.	0-122 S.R.	0-102 R.Re
	0-074 (2) R.Re	0-079 R.Re	0-122 D.R.	0-102 S.R.
Rapid re-excitation the invariable response.	0-071 D.R.	0-078 S.R.	0-114 R.Re	0-102 S.R.
	0-070	0-074	0-113 S.R.	0-102 S.R.
	0-068	0-070	0-105 (2)	0-094 (2)
	0-061	0-062	0-098 (2)	0-087 (2)
	0-052	0-056	0-090 (2)	0-079 (2)
	0-046		0-083 (2)	0-072 (2)
No response to second shock.	0-038	0-049	0-076 (4)	0-064 (2)
	0-030	0-041		0-056 (2)
	0-027	0-032	0-067 (2)	0-049 (2)
	0-022	0-025	0-060 (2)	0-041
	0-019	0-019	0-053	0-034 (2)
				0-026
No response to second shock.	0-018	0-014		0-022 (2)
	0-016	0-013	0-033	0-018 (2)
	0-014	0-009	0-030	0-016
	0-013	0-007	0-027	0-015
			0-024	
			0-020	
			0-017	
			0-013	
			0-010	

\* Either single or double responses.

† The number in brackets indicates that the observation was repeated.

coupled shocks are thrown in when the auricle has been brought to a complete standstill by vagal stimulation. The reactions are stated in Table II. They are similar to those last described. If the second shock falls during the period of absolute refractoriness which follows response to the first shock (a period varying from 0-017 to 0-043 of a second) it fails to yield a second response. If the two shocks are separated by greater time intervals, the multiple response is constant up to certain time limits (varying in our experiments from 0-070 to 0-109 of a second from the beginning of the cycle). If the separation of the shocks is greater still the reaction becomes variable; over a period of about 0-02 of a second, single, double and occasional multiple responses are seen. When the interval between the shocks is greater than about 0-10 (exceptionally 0-130) of a second, the second shock, like the first,

always yields a single response. Examples of the curves are shown in Figs. 6, 7, 8 and 9. In each of these figures the top record signals the break shocks. The downward movement of the string signals the first, and the returning or upward movement of the string the second break shock. The lower records show the response of the auricular muscle, and were recorded from paired contacts placed directly upon the muscle. In each instance the auricle was fully under the influence of the vagus. In Fig. 6 the two break shocks fall with an interval of 0.0149 of a second between them and a single response (*a*) is shown. The interval of stimulation is widened to 0.0183 of a second, and the response is multiple (*a*, *b*, *c*, *d*, etc., of Fig. 7). The interval is gradually widened further (Table II, Dog *MO*) and the multiple responses are invariably obtained up to 0.0942 of a second (Fig. 8). In Fig. 9 the interval is 0.1030 of a second, and a single response (*b*) to the second shock is shown.

An example of double response to the second shock is shown in Fig. 14. The first shock yields response *a*, the second shock, falling 0.094 of a second later, yields responses *b* and *c*.

### *The mechanism.*

However produced, the state of rapid re-excitation is of the same nature. The rate of beating rises abruptly and very considerably; it continues so long as the vagi are stimulated. The maximal rates attained may be 3,000 or even 3,500 per minute; usually they range from 1,500 to 2,500 a minute. The rate of rapid re-excitation falls gradually when vagal stimulation is withdrawn and the auricle breaks back either to normal rhythm, flutter, or fibrillation, as has been described previously.<sup>4</sup>

The following examples of the actual mechanism during the rapid action will suffice as illustrations. The top string in Fig. 12 records the rhythmic and occasional testing shocks; the record also shows electrograms from two pairs of contacts placed on the right auricle, in line with the point stimulated (*P* being from the pair proximal, and *D* the pair distal, to the point stimulated). The *Z* contact of each pair lay towards the point stimulated and the contacts were separated by a distance of 8 mm. The auricle responds regularly to rhythmic break shocks (*rb*); an extra break shock (*b*) falls just before the third rhythmic shock of the record, and these together set up the state of rapid re-excitation.\* The record consists of a series of rapid intrinsic deflections. As these succeed one another, the rate increases, until at the end of the curve it has risen to about 1,600 per minute. Throughout the whole of this curve the deflections maintain a constant direction, all the excitations which they represent proceed from the direction of the point originally stimulated and travel over the line of the four contacts, striking

\* In Table I we do not enter examples of this kind, but only those in which the occasional shock is coupled with the preceding rhythmic shock.



them in the order of their proximity : it is a relatively simple example. The lengths of the cycles of the two curves are written above each, and the transmission intervals between. These readings and their continuation are given in Table III (*MI*, 4).

It is to be emphasised that the excitation wave which strikes the proximal contact is the same as that which strikes the distal one : this is indicated by the lengths of the cycles in the two curves. These vary together in length : thus, the 9th cycle in each curve is of unusual length and measures 0.073 of a second. It is also to be noticed that the transmission intervals remain constant throughout that portion of the record upon which they are written, and that they are of the same value as the transmission intervals prevailing when the auricle was responding to the preliminary rhythmic shocks. In this instance it is clear that the area originally stimulated is also the area from which the waves are propagated during the state of rapid re-excitation. The maintenance of the original transmission intervals in this record is of interest because it suggests that, although the rate of beating has increased from 197 to 1,415\* per minute, the rate of fibre conduction has remained almost undisturbed. We say "undisturbed" because the intervals are so constant, we say "almost undisturbed" because the deflections are not quite constant in amplitude and form : the excitation waves all start from the same point, or from the same small area, and the variations in amplitude are to be ascribed to slight aberrations of the waves as they cross the contacts, aberration which is sufficient slightly to modify the form and height of the deflections, but insufficient materially to change the intervals of transmission. The later transmission intervals (see Table III) increase slightly but definitely in length as the rate further advances, thus confirming the view that aberration is happening. Curves such as these distinctly suggest that, providing the refractory period is sufficiently reduced, the auricular muscle is capable of conducting excitation waves unimpairedly over distances of at least 8 mm. at rates up to 1,400 per minute. The curves cannot be held to prove this, but they strongly suggest it, and thus lend support to the evidence which we have previously obtained, namely, that changes in conduction manifested at and induced by high rates of beating are always brought about by conflict between the crest of the excitation wave and the partially refractory muscle. The present curve is to be explained on this basis : the auricle appears to be conducting impulses at a little more than the maximal rate at which conduction can be carried on unimpairedly. The waves are flowing through tissue in a state of very partial refractoriness.

Fig. 10 is a second example, being taken in similar circumstances from another animal and showing very similar events. The state of rapid re-excitation is set up by a single make shock (*m*) following shortly upon a rhythmic break shock (*rb*). The direction of the intrinsic deflections is maintained and the transmission intervals remain constant for a few cycles :

\* This rate is calculated from the cycle, which has a length of 0.0424 of a second.



body of the auricle and the other upon the inferior cava, the two pairs being in line with the point stimulated and 20 mm. apart. The right auricular appendix was stimulated with rhythmic shocks at a rate of 190 per minute: and the rapid re-excitation was started by means of a single shock to which the first premature deflection (*c*) is a response. The responses to the rhythmic shocks and to the single shock appear as excitation waves (*b-c*) which flow directly over the four contacts, as indicated by the broken arrow in the diagram of contacts to the right in Fig. 1. The rate at which these four excitation waves are transmitted across the contacts is identical. The first re-entrant wave takes a different direction, as do all those which succeed it. The original transmission interval of 0.03 of a second changes to a minus quantity of 0.0035 of a second. The intervals remain at about zero for the rest of the chart. The excitation waves strike the inferior caval contacts in the original direction, they strike the contacts on the body of the auricle in a reversed direction. Briefly, the excitation waves now come from the muscle between the two pairs of contacts and spread centrifugally from this central region (the course marked by the unbroken arrows in the diagram of contacts). It is, of course, conceivable that the re-entrant waves, which strike the contacts from a new direction, may have come originally from the appendix, swerving in their passage: but it would be necessary to assume a swerve too constant in type to admit this explanation. It is far more probable that the rapid re-excitation actually originates in the mid region in this instance. In support of this contention is the fact that the change of direction comes with the first spontaneous beat of the auricle (*i.e.*, *f*, that which follows the response (*c*) to the premature shock). In further support is the definite pause (0.00999 of a second) which precedes the first deflection of the rapid re-excitation in the auricular curve: for such a pause would be anticipated if re-entry was affected at some distance from the point stimulated. A similar pause, followed by a state of rapid re-excitation, during which there is from the first a reversed direction of the deflections, is to be seen in Fig. 8 (between deflections *b* and *c*).

*Distance travelled by the waves.* In discussing Fig. 12, it has been pointed out that each wave is represented in two records taken from points 8 mm. apart. In the case of Fig. 11 the distance was greater, namely, 20 mm. In several experiments we have placed a pair of contacts on the inferior cava, beyond the reflection of the pericardium, and another pair on the tip of the right appendix. If the state of rapid re-excitation is now set up by stimulating the body of the auricle, it is found that the waves which reach the widely separated recording contacts always correspond. We illustrate this statement by Fig. 13 and Table IV. In Fig. 13 the auricle is responding to rhythmic break shocks (*s*): a single extra shock (*o*s) falls a little before the fourth rhythmic shock, and these together set up the rapid re-excitation. The analysis of this curve is given

in Table IV. If the interintrinsic intervals of the two columns (*S. I. C.* and *App.*) are examined it will be seen that corresponding variations in length are found in the two curves; they do not correspond precisely, it is true—that is not to be expected—but they correspond more than sufficiently to establish our conclusion. We find this correspondence, when separate regions of the auricle are compared, to be invariable whenever the curves are of sufficiently simple form to permit analysis; it is certainly present up to rates of approximately 2,000 per minute, and very probably extends beyond this range. The beating of the auricle as a whole during the state of rapid re-excitation thus proves to be a co-ordinate one.

*Conclusion at high rates.* It has been stated that frequently at the onset of the state of rapid re-excitation, the transmission intervals remain constant, although the rate at which the auricle beats rises from 200-300 per minute to 1,000 or 1,400 per minute. From this it has been inferred that the fibres, while under the influence of the vagus, are able normally to conduct impulses at these very advanced rates. But the inference does not constitute proof, for it is not certain that at the low and high rate of beating the excitation waves pursue precisely the same course across the contacts. To investigate this matter further we place two pairs of contacts upon the auricle in line with a pair of stimulating electrodes, and proceed to stimulate rhythmically at advancing rates while the auricle is kept fully under vagal stimulation. As stated at an earlier stage, it is essential that the vagi should be stimulated first and that the refractory period be reduced to and maintained at a minimal point before the rhythmic shocks are allowed to enter the muscle; otherwise a state of rapid re-excitation is set up long before the maximal rate of rhythmic stimulation, to which the auricle is capable of responding, is reached. A single record (Fig. 15) may suffice as an illustration of our table. It shows the auricular muscle responding regularly to rhythmic shock at a rate of about 880 per minute. The shocks (*s*) are shown on the curve from the proximal contacts (*P*) and the sixth and succeeding shocks were allowed to enter the auricular muscle while the latter was at a standstill under vagal stimulation. Providing the precaution named is observed, the rate to which the auricle will respond regularly can be shown to surpass 1,000 per minute (see Table V). The maximal rate attainable varies in different experiments, it lies above 600 per minute; and may be as high as 1,100 per minute. The degree to which the rate may be raised is limited eventually by the onset of the state of rapid re-excitation: at the highest rates of stimulation the auricle responds for a short while (there may be six, ten or more regular responses) and re-excitation supervenes and brings the observation to an end. The transmission intervals may be measured over long stretches of curve at rates slightly below the maximal limit, and over the opening stretch of curve at the maximal rate: as Table V shows, they manifest no increase, remaining uniform from the lowest to the highest rates of rhythmic response recorded. Thus it is proved that the



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TABLE V.

*Conduction under vagal stimulation, at high rates of rhythmic stimulation. Muscle investigated, body of right auricle, length 8 mm.*

Dog M M.		Dog M N.		Dog M O.		Dog M P.	
Rate of stimulation.	Transmission time.	Rate of stimulation.	Transmission time.	Rate of stimulation.	Transmission time.	Rate of stimulation.	Transmission time.
330	0.0167	360	0.0107	536	0.0202	376	0.0103
400	0.0164	390	0.0115	632	0.0188	636	0.0085
450	0.0160	400	0.0112	765	0.0152	784	0.0105
470	0.0161	632*	0.0109	828	0.0164	1040*	0.0105
500	0.0156			830	0.0158		
551	0.0164			1100*	0.0153		
622	0.0168			1100*	0.0166		
706	0.0168						
876	0.0157						
876	0.0160						
1100*	0.0159						

\* Rapid re-excitation occurred after the auricle had responded regularly for a short while.

auricular muscle fibres are capable of unimpairedly conducting excitation waves which follow each other at rates up to 1,100 per minute. That they are capable of normally conducting for short distance waves which succeed each other even more rapidly is highly probable, if not certain. We have examined a large series of the plates upon which our observations<sup>3</sup> on the length of the absolute refractory period under vagal stimulation are based, and have measured the stimulus to intrinsic intervals of the premature responses. These premature responses are responses to the single interrupting shocks thrown into an auricle which is responding regularly to rhythmic stimulation, and these single shocks fall with varying time relations to the last rhythmic shock. The stimulus to intrinsic interval of the premature response remains unchanged until the interval, between the shock yielding this premature response and that which yields the preceding rhythmic response, is reduced almost to the length of the absolute refractory period. It is thus shown that normal conduction over short stretches of muscular tissue may prevail, when a second wave succeeds a first by so short a time interval as 0.03 or 0.04 of a second, intervals which are equivalent to rates of beating up to 1,500 or 2,000 per minute.

In the light of these facts we may conclude that there is no known rate of response at which the rate of *fibre conduction* is depressed; and that, providing the refractory period be sufficiently reduced, the auricular tissue will normally convey excitation waves for long distances when the excitation waves succeed each other as rapidly as 1,000 beats per minute, and for short distances when they succeed each other at rates of 2,000 per minute. We further draw the general conclusion that *the speed of conduction through a fibre is uninfluenced by the rate at which excitation waves succeed each other in*

*passing through it; conduction or non conduction, is controlled in these circumstances solely by the length of the fibre's refractory period. If the fibre responds at all it will conduct, and it will conduct at a normal speed.*

While, on the one hand, we possess what we regard as conclusive evidence that fibre conduction in the mammalian auricle is unaffected by the rate of its response: on the other hand, there are abundant evidences that under vagal stimulation there is a limit to the rate at which impulses are successively and normally transmitted from point to point in the auricular muscle. When the state of rapid re-excitation sets in and the rate of response rises to about 1,000 or more per minute, the deflections of the electrocardiograms are never regular in amplitude. Exceptionally they may be nearly so at rates up to 1,500 (see Fig. 13), but the regularity is not quite perfect. Even at lower rates, irregularity of amplitude may be seen: thus in Fig. 15, although the auricle is uninterruptedly responding to rhythmic shocks at a rate of 880 per minute, the height of the deflections is not quite constant. These variations in amplitude are parallel to those which are seen when, vagal tone being normal, the auricle is responding to much lower rates of stimulation. The last have been subjected to close study, and it has been concluded that they are due to refractory islets or isolated refractory fibres which remain unresponsive as the excitation wave passes. Thus, similar phenomena are witnessed when the uninfluenced auricle is responding to rapid and rhythmic shocks, and when, under vagal stimulation, it is responding to impulses at extreme rates. As the rate is raised, the curves become irregular, and, simultaneously or at a slightly higher rate of response, distinct evidence is obtained that the course of the waves is no longer linear but sinuous. Now it is scarcely to be doubted that the two series of parallel events are brought about in similar fashion, and that the irregularity in the curves of rapid re-excitation is also due to small barriers of refractory fibres. The difference between the two forms of response is chiefly one of rate, and is controlled by the duration of the refractory periods in and out of vagal inhibition. Thus we are brought to the conclusion that although, when the vagi are stimulated, the absolute refractory period of the muscle is greatly reduced, yet it is terminated by a period of partial refractoriness; and that, if the rate of response is sufficiently high, the impulses enter muscle in which certain fibres have not yet regained their responsiveness, the wave in travelling avoiding these fibres and thus acquiring its sinuous course. There appears, however, to be some difference in the constitution of this partial refractoriness in and out of vagal inhibition. When the auricle is not under the influence of the vagus and the rate of rhythmic stimulation surpasses 200 per minute, the state of partial refractoriness varies sufficiently in its density from cycle to cycle to yield discrepancies in the readings of the absolute refractory period. These discrepancies, or overlaps, in the readings are well displayed in Table II of a former paper;<sup>3</sup> they are confined to the earliest phases of recovering responsiveness. In measuring the length of the absolute refractory



period under vagal stimulation such discrepancies are rarely seen\* (see Table I of the earlier paper<sup>3</sup>; in Table I of the present paper the discrepancies are omitted). It is necessary, therefore, in postulating a partially refractory period, as an explanation of irregularities in the two circumstances, to acknowledge that under vagal stimulation the partially refractory period which is developed is less dense, or at the least to assume that that phase of it which is most dense is of very fleeting duration. Except for this qualification† the two partially refractory states of which we speak appear to be alike.

*The origin of the state of rapid re-excitation.*

A chief and necessary factor in the production of the state of rapid re-excitation is a greatly reduced refractory state. Evidence for this has been brought forward in this and several previous papers; perhaps the most convincing argument is that there is a distinct relation between the rate of beating which the auricle attains and the degree to which the refractory period is reduced; the average figure to which this reduction occurs is 0.025 of a second, and when such a refractory period prevails the auricle is capable of responding (theoretically) at a rate of 2,400 or a little less: if the refractory period becomes more greatly reduced then the possible rate of response is higher. Exceptionally the refractory period may fall to 0.014 of a second, and theoretically it is then capable of responding at a rate of nearly 4,300 per minute. At other times the fall is less, and exceptionally may be no further than to 0.038 of a second, the potential rate of response being about 1,580 per minute. The usual rates of rapid re-excitation when the muscle is under full vagal control lie between 1,500 and 2,500 per minute. The extreme rate may be shown to be associated with greatly reduced, and the less extreme with the less reduced, refractory periods. Thus the rates attained are those which are to be anticipated if re-excitation occurs shortly after the completion of the absolute refractory periods of preceding responses.

Nevertheless a simple reduction of the refractory period is insufficient to provoke the state of rapid re-excitation. In general it is necessary that two successive shocks‡ (isolated, or part of a series) should fall sufficiently near together. It is the second shock which provokes the multiple response or "after effect" of stimulation. It has been shown that this second shock must fall within a critical period, and that, falling within this period, the state of rapid re-excitation is always produced by it. The critical phase is the phase of the cycle corresponding to the partially refractory period. This relation is most clearly shown by experiments in which the vagus is first stimulated and the auricle is then submitted to rhythmic stimulation at

\* Though they do occur from time to time.

† And a further qualification in respect of the manner of production, to be discussed presently.

‡ The exception, if it be a true exception, is found in those rare experiments in which the normal rhythm is converted to rapid re-excitation by vagal stimulation.

advancing rates. The auricle responds to these, and up to a point the electrical responses are uniform in amplitude: when the rate is sufficiently advanced to render the intrinsic deflections irregular in height or form, then it is the rule that rhythmic stimulation at this rate cannot be long maintained without the auricle breaking into the state of rapid re-excitation.

In a previous article<sup>3</sup> it has been concluded (page 132) that flutter is provoked when an effective shock enters auricular muscle while the latter is in a critical condition, and that this condition is a state of partial refractoriness. A parallel conclusion applies to rapid re-excitation. Each form of after-effect, namely, flutter and rapid re-excitation, is provoked by a stimulus which enters muscle which is partially refractory. Rapid re-excitation is in fact equivalent to flutter upon a diminutive scale, the last conditioned by the greatly reduced absolute refractory period. Rapid re-excitation is to be regarded as due to a small circus movement from which centrifugal waves spread over the whole surface of the auricle. The gradual increase in the rate of a fluttering auricle under vagal stimulation, an increase which occasionally progresses until it reaches that of the state of rapid re-excitation proper, also speaks strongly for this view.

The state of rapid re-excitation is set up when the second stimulus enters the muscle at any period from the end of the absolute refractory period up to a point about 0.07 or 0.08 of a second, or a little longer, from the beginning of the cycle. The critical phase lasts some 0.05 to 0.06 of a second, as a rule, and this we consider to be the measure of the partially refractory period under vagal stimulation. If vagal tone is normal, a partial refractory period does not appear except when the rate of rhythmic response is much raised: its appearance under vagal stimulation is independent of the rate of stimulation; each response of the muscle, however long the period of rest which precedes it, has this sequel. It is to be explained by supposing that the individual fibres of the auricle are not equally affected by vagal stimulation, that in some the contraction process is more depressed, and that in these the refractory period is shorter than in others.

The size of the circuit which underlies rapid re-excitation may be gauged approximately. Assuming that the transmission rate from point to point is about half the normal, *i.e.*, about 400 mm. per second, then the circumference of the circuit carrying 3,000 to 2,000 waves per minute would be of 8 to 12 mm.: it would have a diameter of 2.5 to 3.8 mm. Obviously these circuits must be supposed to establish themselves in the muscle of the wall, rather than around the mouths of the vessels; sometimes the focus originating the rapid waves lies near the point stimulated, in other instances it lies at a distance. This is evidenced by the waves sometimes coursing over the recording contacts in the same direction as those directly provoked by the initial stimulation (Fig. 12), while at other times the direction of the waves becomes reversed over the contacts once rapid re-excitation sets in. The pause, which often succeeds the second shock

(Figs. 8, 11 and 13), a pause which is often conspicuous, is probably attributable to the interval of delay while the second wave travels from the point of stimulation to the area in which the circus is set up, and in the return of these waves to the recording contacts. The length of this pause is independent of the degree of prematurity of the second response, but tends to remain constant in length, providing that the records of the rapid re-excitation, set up subsequently, remain constant in form.

There is no difficulty in conceiving small circuit movements in such a sheet of muscle as the auricle presents, though necessarily the conception remains largely hypothetical. The muscular layer consists of freely interlacing and overlapping strands of branching fibres. Thus, supposing in such an interlacing network an excitation travels along the strand *a* (Fig. 2), and in natural circumstances divides along the two limbs *b* and *d*: then the two



Fig. 2.

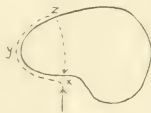


Fig. 3.

Figs. 2 and 3. Two diagrams to illustrate the manners in which, as it is conceived, small circus movements may become established in the auricular muscle.

crests will meet somewhere in limb *c* and will be brought to a standstill. But if, on entering, the wave finds the muscle at *e* refractory, it will be deflected along limb *b* only and, passing through *c* and *d*, may find the muscle in *a* responsive on its return. Or again, in muscle represented as a more uniform sheet, an excitation wave in its progress may meet an area of still refractory muscle at *x* (Fig. 3). In that case it will creep around the edge (*x y z*) of this refractory area, until at last, owing to the delay while it travels, it will find at some point *z* that the muscle has now recovered. Entering *z* it will find the muscle in front of it responsive during its passage back to *x* where, if the time conditions are suitable, it may re-enter the same course. Consideration will show also that once re-entering, the course which the wave pursues on its second journey will be the course which it has prepared on its first: the circuit when once established will tend to persist without very material variation. The advancing wave tends to follow closely on the wake of its own retreat, the gap of responsive muscle in the circuit remaining minute.

TABLE VI.

*Refractory period of rapid re-excitation.**Dog M.A. (Record 14.)**Rate per minute, 1,445. Average length of cycle 0.415 second.*

Time from first intrinsic to stimulus. In seconds.	Length of corresponding cycle. In seconds.
0.0016	0.0418
0.0082	0.0423
0.0171	0.0410
0.0266	0.0428
0.0274	0.0433
0.0282	0.0430
0.0282	0.0423
0.0316	0.0420
0.0367	0.0420

When waves of excitation succeed each other at rates of 1,500 and over in the auricle, the responsive stage is too short to be demonstrable. We have repeatedly observed that rhythmic shocks, which are allowed to enter the muscle after the state of rapid re-excitation is set up (see Fig. 12), are without influence upon the condition. A single illustration of this observation may suffice (Table VI). In the first column of this table are given the intervals between the first of two succeeding intrinsic deflections (during a period of rapid re-excitation) and the rhythmic shock which subsequently falls upon the muscle; in the second column are given the lengths of the corresponding cycles. These are uninfluenced by the electrical stimuli, although these fall at all phases of the cycles.

## SUMMARY OF CONCLUSIONS.

1. The state of rapid re-excitation is described in detail. When established, it is a condition in which the auricle is re-excited at extreme rates, ranging from 1,500 to 3,500 per minute. The waves are carried over the whole auricular tissue, which thus beats co-ordinately; but the waves are more or less sinuous in their courses.

2. This state of rapid re-excitation can be produced only in auricles in which the refractory period has been greatly reduced. It is provoked in these when two shocks enter the muscle, the second falling during a critical phase. This critical phase lasts usually some 0.05 to 0.06 of a second and is constituted by a partially refractory condition of the muscle.

3. Thus, the state of rapid re-excitation is in many ways comparable to flutter, though its scale is diminutive, owing to the greatly reduced refractory period. The underlying cause is almost certainly a small circus movement in a muscle area of a few millimetres diameter.

4. The sinuous course of the waves is comparable to that which is seen in impure flutter, and is attributed to similar causes, namely, to the waves meeting islets of refractory tissue in their passage.

5. Providing that the refractory period of the auricle is sufficiently reduced, the muscle is capable of conveying excitation waves at a natural speed, when these waves succeed each other up to rates of 1,100 per minute: waves succeeding each other at even higher rates are conveyed normally for short distances.

6. The speed of conduction through an auricular fibre is uninfluenced by the rate at which the waves succeed each other in passing through it. Conduction or non-conduction is controlled in these circumstances solely by the length of the fibre's refractory period. If the fibre responds at all it will conduct, and it will conduct at normal speed.

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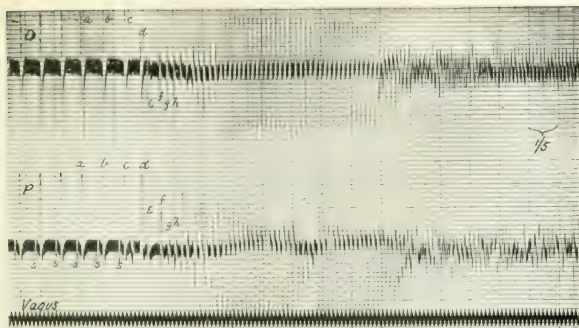


Fig. 4. *Dog M.K. (Record 4.)* Simultaneous electrograms from two pairs of contacts (*P* proximal and *D* distal) placed in line with stimulating electrodes. The auricle while under strong vagal stimulation (right) is responding regularly to rhythmic break shocks (as applied to the tip of the right appendix, as indicated by the serial intrinsic deflections *a, b, c, d*). The *Z* contact of each pair was towards the point stimulated. Suddenly the auricle breaks *e, f, g, h* into a state of rapid re-excitation which continues to the end of the plate. The rate rises quickly to 2,000 beats per minute. Time lines in fifths and tenths of a second.

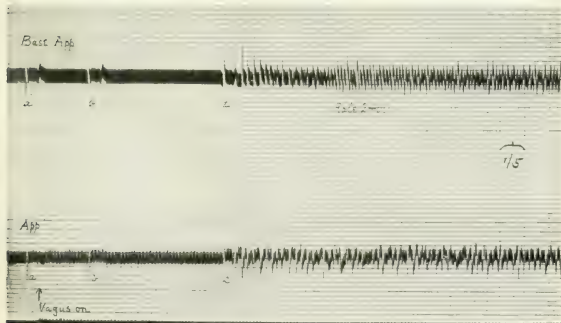


Fig. 5. *Dog M.J. (Record 11.)* Simultaneous electrograms from two pairs of contacts, placed in line on the base and tip of the right appendix, the *Z* contacts being towards the pacemaker. When the right vagus is stimulated the auricle which is responding regularly to its normal impulses (intrinsic deflections *a* and *b*) slows down (deflection *c*) and then breaks abruptly into a state of rapid re-excitation. Time lines in fifths and tenths of a second.





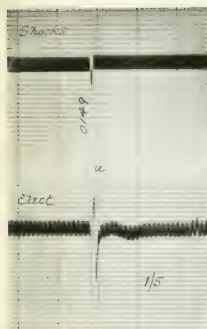


FIG. 6.

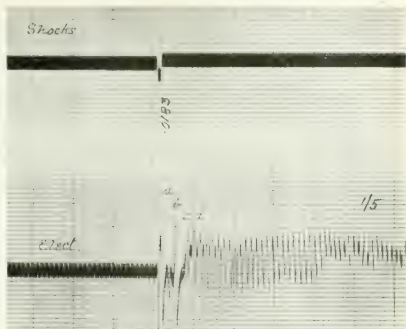


FIG. 7.

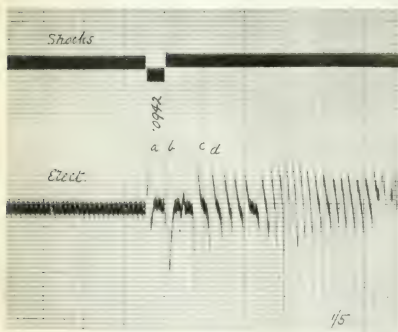


FIG. 8.

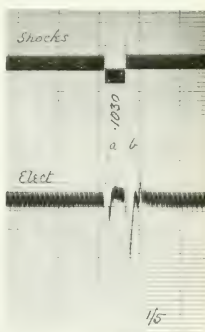


FIG. 9.

Figs. 6, 7, 8 and 9. *Dog M O*. (Records 1, 3, 11 and 13.) Four similar records from one experiment. The top curve in each is the signal of stimulation; a downward movement of the string indicating the first and an upward movement the second break shock. The bottom curve of each is an electrogram taken from the right appendix; the Z contact being towards the tip of the appendix. These curves illustrate the different reactions obtained when, under right vagal stimulation, the faradic current is shown on the electrogram; two break shocks are applied to the tip of the appendix at varying time intervals from each other. Time in fifths of a second.



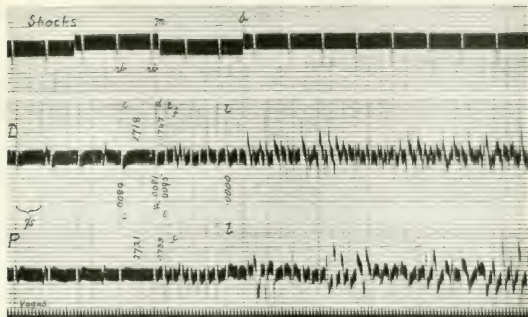


Fig. 10. *Dog M I. (Record 33.)* Traces under right vagal stimulation. The top curve signals the shocks, the middle curve the response of the heart to shocks. The lower curves are the heart's response to shocks from two years of control placed by the heart's right appendix. *P*—response from contacts proximal to and *D*—response from contacts distal to point of stimulation, i.e., the tip of the right appendix. The *Z* contact of each pair gives a response from the tip of the appendix. Time in fifths and tenths of a second.

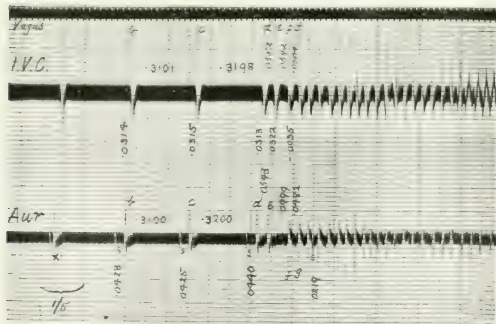


Fig. 11. *Dog M I. (Record 16.)* This record is charted in Fig. 1. Similar electrograms, from the inferior cava and body of the right auricle, taken while the auricle was under right vagal stimulation, and responding (*b, c, d*) to rhythmic break shocks (*s*). A single break shock (not signalled in the figure) gives a response *c*, and a state of rapid re-excitation follows. The *Z* contact of each pair lay towards the tip of the right appendix, the point stimulated. Time in fifths and tenths of a second.



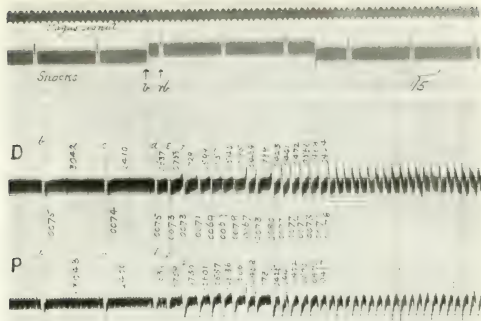


Fig. 12. *Dog M.I. Record 4.* The record shows the signal of rhythmic break shocks and two second make or break shocks, and simultaneous electrograms from four contacts including the right auricle. *P*—curve from contacts proximal to and *D*—curve from contacts distal to point stimulated (the Z contact of each pair lay towards the point stimulated). The lengths of cycles are written directly above each in the two curves, and the transmission intervals are written below curve *D*, in decimal points of a second. Record taken under right vagal stimulation. Time in fifths and tenths of a second.

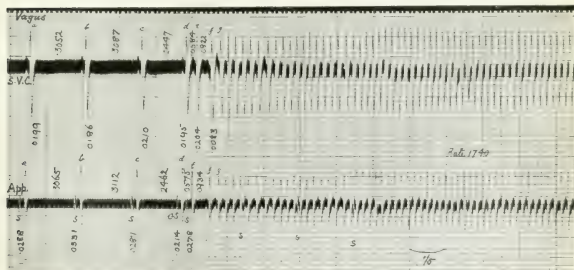


Fig. 13. *Dog M.I. Record 15.* Taken under right vagal stimulation. Simultaneous electrograms from the superior vena cava, extraperitoneal and right appendix. The body of the auricle was stimulated by means of rhythmic break shocks *et c.* A single make shock falls just before the fourth rhythmic shock and the latter sets up rapid re-excitation. The superior caval and appendicular waves correspond throughout the whole curve. The Z contact of both pairs was towards the point stimulated. Time in fifths and tenths of a second.



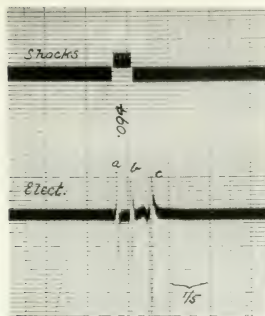


FIG. 14. *Dog M.L. R. 114.* A similar record to those of Figs. 6 to 9. The first break shock yields a response *a*, the second break shock yields two responses, *b* and *c*. Time in fifths and tenths of a second.

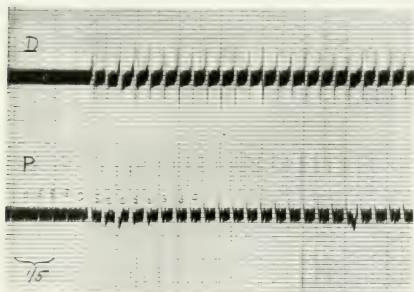


FIG. 15. *Dog M.M. R. 1133.* Simultaneous electrograms from the animal taken from paired contacts (*P* = proximal and *D* = distal to the point stimulated). The auricle responds to shocks succeeding each other at a rate of 880 per minute. The shocks are signalled upon the proximal record; the sixth and succeeding shocks were allowed to enter the muscle. Time in fifths and tenths of a second.





## A DEMONSTRATION OF CIRCUS MOVEMENT IN CLINICAL FLUTTER OF THE AURICLES.

By THOMAS LEWIS, A. N. DRURY and C. C. ILIESCU.\*

(*University College Hospital Medical School.*)

EXPERIMENTS upon dogs have led to the conclusion, fully described in preceding articles in this journal, that flutter of the auricle, as it occurs in man, consists of a circus movement of the excitation wave around some natural ring of muscle in that chamber.<sup>2</sup> Based upon animal experiment, this conclusion has so much evidence to support it that little doubt exists in our minds that it may be regarded as arriving at a degree of finality: but in that it has so obvious a bearing upon practical medicine we have felt that every endeavour should be made to render it secure by further distinct tests. It has occurred to us that direct evidence might be obtained from patients affected by this curious disorder.

If in clinical flutter a central excitation wave circulates continuously around a fixed muscular path, the general direction of its movement in the auricle may be expected to change from instant to instant in a special manner. We are lead to expect that the average direction of movement will alter gradually, turning consistently in one or other direction through 360 degrees and repeating this revolution. It is not to be expected that this change will be perfectly smooth and uninterrupted, for the auricle is neither a flat ring nor cylinder of muscle, but an irregularly shaped mass, and the wave moves not only on the central path but sends centrifugal offshoots into outlying portions of muscle, such as those which clothe the cavæ and constitute the appendages. Nevertheless, if the wave continuously follows a central circular or elliptical path, it will decidedly influence the general direction of movement. Now when the average movement is progressing in a particular direction, say from right to left, then the distribution of potentials in the muscle is known by experience to be such that the muscle elements which lie to the right are relatively negative to those which lie to the left: the electrical axis in these circumstances will set from right to left, pointing in the general direction in which the wave is tending to move. The changes in

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\* Working on behalf of the Medical Research Council. A preliminary report of these observations appeared in the Proceedings of the Physiol. Soc., March 12th, 1921.

direction of the electrical axis during the progress of a flutter cycle should therefore indicate the changes in the direction in which the excitation wave travels.

In auricular flutter, where we suppose the direction of movement to alter through 360 degrees, we should expect to find a similar rotation of the electrical axis, providing that the leads from which the electrocardiographic curves are taken are suitably arranged: the rotation should be most conspicuously shown in curves taken simultaneously from leads lying in the plane in which the central wave is travelling.

Theoretically, if the wave of excitation travels along a circular path and the movement is confined to one plane, as it would be in travelling through a flat ring or an undeformed cylinder of muscle, and if simultaneous curves are taken from three leads, arranged in the manner of Einthoven, from the angles of an equilateral triangle lying in this plane: then the curves from each lead will be similar in form: each will be a *sine* curve, a rounded summit above the zero line followed by a rounded dip of similar though inverted form below the zero line. But the summits on the one hand and the dips on the other, in the simultaneous leads, will not be synchronous: they will show overlap, amounting to 16 per cent. of the cycle when either leads *I* and *II*, or leads *II* and *III* are compared, and to 33 per cent. of the cycle when leads *I* and *III* are compared. The direction of overlap will depend upon the direction in which the wave is revolving. Simple *sine* curves with these precise overlaps are not to be expected when the wave is circulating in the auricle, and this for several reasons.

(a) As has been pointed out, the muscle has not a regular form: the circular movement is therefore not entirely confined to one plane: and, in addition to the central movement, there are the centrifugal paths which will influence the resultant curves.

(b) The movement is not necessarily, nor probably, circular. If it is assumed to include the mouths of the two cavæ, it will more probably be elliptical or irregularly elliptical.

(c) The circular movement projected to a single plane, which diverges somewhat from the plane of this movement, will appear elliptical: an elliptical movement for the same reason will appear as a narrower ellipse. In this connection it is to be stated that in leading off it is unlikely that the precise plane of the circus movement will be chosen.

#### OBSERVATIONS.

In making our observations we have considered it more desirable to investigate thoroughly a single case of clinical flutter, rather than to study less fully a number of such cases. We are indebted for the case which will be described to Dr. John Parkinson.

The patient, a small man of 61 years, is known to have suffered from auricular flutter since 1913; his symptoms commenced some eighteen

months prior to this date. His auricular rate while under our observation has been almost constantly 245 per minute, and the ventricular rate precisely half the auricular rate. He is breathless on slight exertion and speaks of a sense of constriction, accompanied by a little pain, across the sternal region, when he walks sharply. His chest is well built, and measures 33 inches in circumference at the level of the nipples. There is a flattening of the chest wall in the right axilla and some indrawing of the rib spaces. Movement is limited in the right axilla and at the right base; there is dulness to percussion over these regions, the breath sounds are distant and, at the base, a little friction crepitus is heard. Over the remainder of the chest the note is hyperresonant and the breath sounds are harsh. Screening shows increased opacity with limited movement of the diaphragm on the right side.

The cardiac impulse is feeble, and lies in the 5th interspace in the nipple line; the left margin of dulness lies  $\frac{1}{2}$  inch outside the nipple line ( $3\frac{1}{2}$  inches from the middle line), the right margin lies  $1\frac{1}{4}$  inches from the middle line. Screening shows some enlargement of the heart, the ventricles lying in an almost horizontal position. The right auricle projects, more than is usual, to the right side.

The heart sounds, with the exception of a reduplication of the 2nd sound at the apex, are normal (standing and lying). The brachial arteries are tortuous; the systolic blood pressure is 130 mm. Hg.. The liver is not enlarged; the veins of the neck become engorged and some cyanosis of the head develops when he lies quite flat.

To sum up, there are definite signs of some enlargement of the heart; the valves are normal. The heart appears to have been displaced somewhat to the right side, presumably as a result of chronic changes in the right lung and pleura.

### *Leads.*

In leading off from the chest wall we have used circular copper discs 2 inches in diameter, attached to the chest by means of a paste of flour and salt solution; the skin has first been prepared by rubbing it with spirit to remove fat,\* and subsequently soaking it with brine. The electrodes are fastened to the skin by means of adhesive strapping. It has been our care to reduce the resistances of the skin at the contact sites uniformly, thus rendering the resistances of the body in these leads sufficiently equal. These resistances have always been measured and have varied on different occasions from 250 to 750 ohms each. We connect each of the three string recorders to a pair of the three contacts after the manner of Einthoven, Bergansius and Bijtel<sup>1</sup>; the resistances of the three strings used have been 1,900, 1,900 and 1,750 ohms respectively, resistances which have been found to be

\* For this very helpful method of reducing skin resistance we are indebted to the suggestion of Professor Wertheim-Salomonsen.

sufficiently equal for our purposes. The three strings are standardised, so that 1 centimetre excursion is equal to a millivolt in the curves. In this manner we obtain simultaneous and standard electrocardiograms from the three leads.

The chief planes of lead used have been the sagittal, the frontal and the horizontal.

*The sagittal plane.* In this plane we use three contacts, one immediately to the left of the manubrium sterni, one a little to the right of the xiphisternum, and one immediately to the right of the 7th dorsal spine. The plane is not quite sagittal therefore, but inclines a little towards the left shoulder above.

The leads are :—

Lead 1.	Manubrium to xiphisternum	=	$7\frac{3}{4}$ inches.
.. 2.	.. to spine	=	$9\frac{1}{2}$ ..
.. 3.	Xiphisternum to spine	=	9 ..

*The frontal plane.* The three contacts are placed, one on the manubrium sterni, one in the midaxillary line and a little below the level of the left nipple,\* and one an inch beyond and a little below the right nipple.

The leads are :—

Lead 1.	Manubrium to left nipple	=	$8\frac{3}{4}$ inches.
.. 2.	.. to right nipple	=	$8\frac{3}{4}$ ..
.. 3.	Left nipple to right nipple	=	$10\frac{3}{4}$ ..

*The horizontal plane.* The three contacts are placed, one in the mid-axillary line a little below the level of the left nipple, one an inch beyond and a little below the right nipple, and one directly to the right of the 7th dorsal spine.

The leads are :—

Lead 1.	Left nipple to right nipple	=	$10\frac{3}{4}$ inches.
.. 2.	Left nipple to spine	=	$10\frac{1}{2}$ ..
.. 3.	Right nipple to spine	=	7 ..

### *Curves and their analysis.*

*Sagittal plane.* The actual curves obtained in the sagittal plane are shown in Fig. 8. These curves were enlarged 5 diameters, plotted and measured (Fig. 1). The plotted curves (1, 2 and 3) are shown, though they are reduced from the original enlargement in reproduction. Arbitrary base

\* Placed further out than the corresponding right contact to avoid the impulse of the heart.

lines\* are drawn approximately through the centres of the three curves, and the heights and depths, as measured from these lines, are written on the curve in millimetres in the enlargement. It is usually necessary at this stage to move one or two of the base lines a little to obtain a fit. If the curves are to accurately represent the potential differences, then the values in leads 1 and 2, added algebraically, must sum up to the values in lead 2. The fit is accurate with very minor discrepancies in all the charts published, and this speaks for the accuracy with which the curves have been standardised.

The values of the E.M.F. are tabulated for the three leads at each fiftieth of a second throughout the cycle in Table I; the corresponding angle, calculated trigonometrically, which the electrical axis makes with the line of lead 1, is stated in a separate column, as is also the manifest potential ( $E$ ) for this plane. The latter is reduced to decimal points of a millivolt. The calculated angles are shown diagrammatically in Fig. 5, the length of each arrow representing the value of the E.M.F. as it is projected upon the sagittal plane. Against the head of each arrow is set the time in decimal points of a second.

Starting from zero it will be seen that the direction of the electrical axis moves in a clockwise fashion, revolving through 360 degrees and returning to its original point in 0.245 of a second, as the cycle is completed.† The movement is constantly clockwise, with the exception of a small anti-clockwise movement between the times 0.04 and 0.06 of a second: the rotation is particularly clear and uniform between 0.10 and 0.22 of a second. The set of the arrows, representing the electrical axis of the auricles, may be taken as an index of the change which occurs in the general direction in which the excitation travels as the cycle progresses.

A clearer idea of what this rotation may mean is obtained by a different form of illustration. In Fig. 7 arrows of the same lengths and having the same inclinations are drawn, but they are drawn, not from a centre point, but from the margin of an ellipse, with the idea of correlating them with different portions of the auricular musculature. If this diagram correctly represents the events in relation to the auricular muscle, and further evidence that this is so will be given a little later, then the weak axis at 0.00 represents the movement of the excitation wave from the left to the right auricle past the superior cava, the strong axes 0.02 to 0.08 represent its movement down the main musculature of the right auricle, the weak axes 0.10 and 0.12 its

\*The actual base line is indeterminate, because the string never rests in the isoelectric position. Small errors in fixing the correct base lines are probable, large errors are improbable. Small shifts of the base lines will influence to some extent the angles determined from the curve but will not influence materially the general result when these angles are plotted relative to each other. That the assumed base lines are sufficiently accurate is shown by the general agreement of the values obtained in the three planes (see page 352).

† We have drawn a single arrow to represent these two time instants (*i.e.*, 0.00 and 0.245 of a second); actually there is a little divergence between them, the auricular angle at 0.00 being influenced a little, though not greatly, by the simultaneous inscription of the end of the ventricular complex.

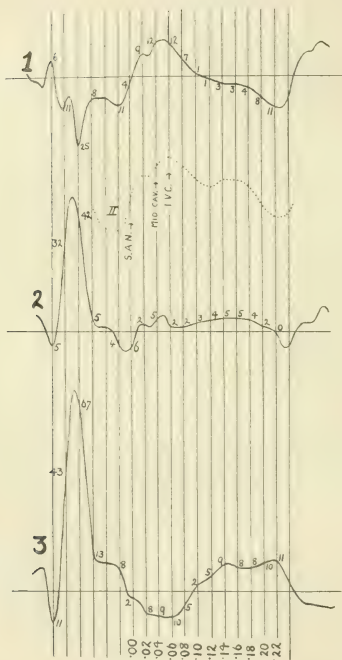


Fig. 1. (Record 3, 23'2-21.) *Sagittal plane*. The outlines of the curves (1, 2 & 3) of Fig. 8. The curves were enlarged originally 7.5 diameters but have been reduced in reproduction. Showing the relative values of the potential differences in the three leads at successive fiftieths of a second. The dotted curve is from the usual clinical lead 2. The times at which the S. A. N. region, mid-caval and inferior vena caval region, become excited, relative to these curves, are indicated.

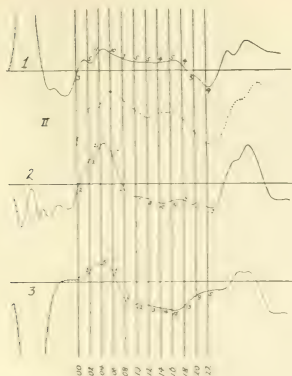


Fig. 2. (Record 10, 23, 2/21.) *Frontal plane.* Similar outlines of the curves (1, 2 & 3) of Fig. 9.

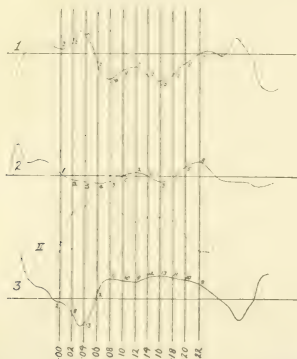


Fig. 3. (Record 3, 30, 3/21.) *Horizontal plane.* Similar outlines of the curves (1, 2 & 3) of Fig. 10. enlarged.

movement back to the left auricle around the inferior vena cava, and the strong axes 0.14 and 0.22 its movement through the main mass of the left auricular muscle. This representation in general agrees with experiments in which the circus movement is around the mouths of superior and inferior vena cava.

*Frontal plane.* The actual curves of the frontal plane are shown in Fig. 9. The enlarged plotted curves are given in Fig. 2 (1, 2, and 3\*) and the angles (calculated in Table II) are represented in Fig. 4. This last diagram shows rotation which is uniform in direction with the exception of a single reversed movement between times 0.14 and 0.16. Compared with Figs. 5 and 7, good agreement is shown: the strong axes 0.02 and 0.06, which are supposed to represent movement in the mass of the right auricle, are directed mainly downward and to the right in the body: the strong axes 0.12 and 0.22, which are supposed to represent movement in the left auricle, are directed upward in varying degrees and to the left.

TABLE I. (*Record 3, 23, 2 21.*)(*Sagittal plane.*)

Seconds.	Leads: E.M.F. in millivolts ( $\times 50$ ).			Angle.	E. in millivolts.
	1	2	3		
0.00	-4	-6	-2	-131°	0.12
0.02	9 10†	2	-8	-19°	0.21
0.04	12 13	5	-9 -8	-8°	0.26
0.06	12	2	-10	-21°	0.26
0.08	7	2	-5	-14°	0.14
0.10	1	3	2	71°	0.06
0.12	-1	4	5	101°	0.11
0.14	-3	5	9 8	112°	0.16
0.16	-3	5	8	112°	0.16
0.18	-4	4	8	120°	0.16
0.20	-8	2	10	139°	0.21
0.22	-11	0	11	150°	0.25

\* These curves were originally enlarged 7.5 times, and have been reduced subsequently.

† The figure which is crossed out is that which represents the original measurement; it has been altered to render the fit perfect for purposes of calculation.



TABLE II. (*Record 10, 23/2/21.*)  
(*Frontal plane.*)

Seconds.	Leads ; E.M.F. in millivolts ( $\times 75$ ).			Angle.	E. in millivolts.
	1	2	3		
0-00	- 3	- 2	1	- 169°	0-04
0-02	5	1½ 11	6	63°	0-15
0-04	11	21	10	58°	0-28
0-06	10	17 16	6	52°	0-22
0-08	7	-2	-9	- 42°	0-13
0-10	5	-7	-12	- 66°	0-16
0-12	5	-8	13	- 68°	0-18
0-14	4	- 10	- 14	- 74°	0-19
0-16	5	- 10	- 15	- 71°	0-20
0-18	4	- 9	13	- 73°	0-18
0-20	- 3	- 11	- 8	- 105°	0-15
0-22	- 5	- 10	- 5	- 120°	0-13

TABLE III. (*Record 3, 30/3/21.*)  
(*Horizontal plane.*)

Seconds.	Leads ; E.M.F. in millivolts ( $\times 75$ ).			Angle.	E in millivolts.
	1	2	3		
0-00	3	1	- 2	- 11°	0-04
0-02	6	- 2	- 8	- 44°	0-11
0-04	10	- 3	- 13	42°	0-18
0-06	- 6	- 4	2	169°	0-08
0-08	- 14	- 3	11	- 162°	0-20
0-10	- 9	0	10 9	150°	0-14
0-12	- 7	2	9	138°	0-13
0-14	- 12	0	12	150°	0-18
0-16	- 1½ - 16	- 3	13	160°	0-23
0-18	- 12	- 1	11	154°	0-18
0-20	- 5	5	10	120°	0-13
0-22	0	8	8	90°	0-12

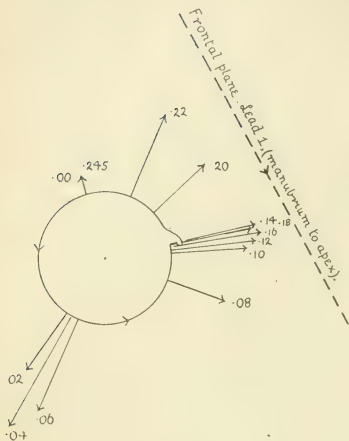


Fig. 4.

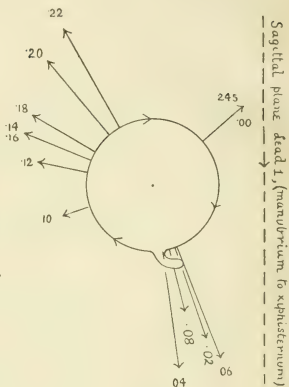


Fig. 5.

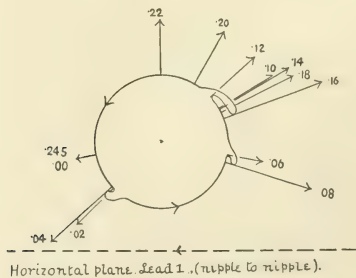


Fig. 6.

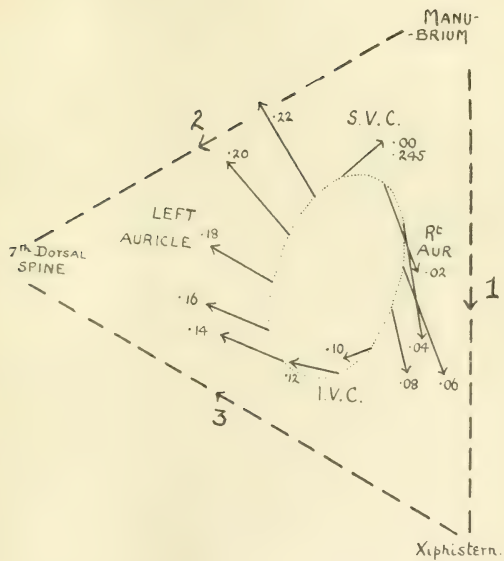


Fig. 7.

*Horizontal plane.* The actual curves are shown in Fig. 10; the enlarged\* plotted curves are shown in Fig. 3; the diagram of angles (calculated in Table III) is given in Fig. 6. This figure also agrees fairly closely with those which have preceded; thus the axes 0.02 and 0.04 are directed forwards and to the right in the body, while those at 0.12 to 0.22 are directed backwards and to the left, as would be expected if these two groups represent movement in the right and left auricle respectively.

*The three planes considered together.*

It has been tacitly assumed that the 0.00 time lines of Figs. 1, 2 and 3, and of the corresponding electrical axis diagrams in Figs. 4, 5 and 6, represent the same time instant in the auricular cycle. That they may not represent exactly the same instant is to be admitted, but the error is not great. The three sets of curves (Figs. 8, 9 and 10) have been orientated into as correct relationship to each other as possible by taking the curve from one lead in each group simultaneously with Einthoven's lead 2 (right arm to left leg). An example of this method of correlating the curves of different planes is shown in Fig. 11. In this record lead 1 of the horizontal plane is taken simultaneously with limb lead 2. The outline of the curve from lead 2 is plotted in its correct position and as a dotted line in the diagram, Fig. 3. The upstroke of the auricular complex begins a little before the 0.00 time line. The outlines of the auricular curves from lead 2 have been similarly plotted in Figs. 1 and 2, thus correlating the whole series.

The general agreement between the angles and E.M.F. values obtained in the three planes is best appreciated by examining Figs. 4, 5 and 6 together. Each diagram represents the set of the angle and the value of the potential difference as this is projected upon the corresponding plane. By combining the direction and values in any two planes, the actual set of the axis relative to the chest wall may be ascertained. By projecting this actual axis on to the third plane, the accuracy of the diagrams as a whole may be tested. In most instances the correspondence is sufficiently close, though naturally there are discrepancies. Thus, the axes 0.22 in Figs. 4 and 5 are in good agreement, the axis projects from below, upwards slightly backwards and slightly to the left in the chest: in Fig. 6, the axis 0.22 shows a backward direction but fails to show, as it should do, the slight inclination to the left. This is a discrepancy, though it is not a serious one; other and similar discrepancies will be found.† The general agreement is sufficient to show the general accuracy of the diagrams and confirms us in the view that the base lines of Figs. 1, 2 and 3 are fixed with sufficient precision.

\* These curves were originally enlarged 7.5 times and have been reduced for publication.

† Discrepancies are likely to be greatest when the axes are weak, for the errors in calculating these are the greatest.

The discrepancies are to be expected, considering that at each stage of the construction errors creep in. The chief sources are in fixing the lines of zero potential difference (base lines of Figs. 1, 2 and 3) in co-relating similar phases of the cycle in curves taken from the three different planes, and in assuming that the leads are taken from the angles of triangles which are exactly equilateral.\*

The movement of the electrical axis in Fig. 5, representing the sagittal plane, is clockwise; in Figs. 4 and 6 the frontal and horizontal planes, it is anticlockwise. This is not an incompatibility, but is dependent upon the actual plane of rotation. The sagittal plane is judged to be the closest of the three used to the actual plane of rotation, not only because the rotation is most uniform in this plane, but because in this plane the values of the potential differences are the greatest. Imagine a ring to be placed precisely in the sagittal plane within the chest, and imagine the movement to be down the anterior limb and up the posterior limb of this ring. Looked at from the right side of the patient, the movement is clockwise: looked at from the front of the patient, the movement is directly up and down, for the ring is seen on edge. Now let the posterior limb of the ring be moved somewhat to the left in the chest: the movement remains clockwise when viewed from the right side of the patient. Viewed from the front, a rotation has now become visible, but, as the posterior limb of the ring lies more to the left in the patient's body than does the anterior limb, and as the movement is up the former and down the latter, it appears as an anticlockwise movement (as shown in Fig. 4).

Let the bottom of the same ring be carried somewhat to the left in the chest (see Fig. 12), and viewed from above the movement is anticlockwise (as shown in Fig. 6).

The diagrams when combined depict the movement in three dimensional space. Viewed from the front the circus lies in the chest as it is depicted in Fig. 12. It is the approximate position of a ring hung around the orifices of the superior and inferior vena cava.\*

A final test completes and confirms, in a striking manner, our demonstration. Our examination of this patient leads us to believe that the excitation wave is circulating around the orifices of the superior and inferior vena cava. According to the relations of the movement expressed in Fig. 7, the relative negativity is at its height in the region of the S.A. node at the time line 0.02: allowing 0.02 of a second for the development of this charge, it should begin to develop in the region of the S.A. node near the zero time line; it should begin to develop in the mid-caval region near the 0.04 line

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\* In the normal chest a line joining the mouths of the two cavæ is vertical or almost so; it may incline above somewhat to the right or left. The plane of the circus as we determine it is tipped perhaps a little too much to the right (in the body) above for the ring to fit accurately to the mouths of the two cavæ, but it is to be remembered that the heart of this patient is somewhat displaced.

and in the inferior caval region near the 0.06 line. These relations are expressed relative to the dotted curve of lead 2 in Fig. 1. The upstroke of this curve represents the movement of the wave down the right auricle. Compare this diagram in so far as it indicates the relation between these points of activation and the curve of lead 2, with the similar diagram. (Fig. 5) of a previous publication.<sup>2</sup> This last diagram relates the curve of lead 2, with the times at which the excitation wave was ascertained to arrive at the muscle points in question, and corresponds to an experiment on the fluttering auricle of a dog, where the excitation wave was moving down the length of the *tænia terminalis*. The relations in the two figures are so closely similar as to leave little doubt that the path and direction of the central wave in our patient has been determined with considerable accuracy.

Finally we publish from the same patient simultaneous curves (Fig. 13) from the three usual clinical leads (1, 2 and 3). We publish these curves because they are in general form similar to those obtained from many patients affected by auricular flutter. In lead 1 the auricular deflections are small, in leads 2 and 3 they are much alike, consisting essentially of a steep upstroke and more gradual decline: the decline, as in many such patients, is broken by subsidiary summits. Our present view is that in all patients who present curves of this type, the circus movement is occurring around the two cavæ and that the direction of movement is down the *tænia* and right auricle and up the body of the left auricle. The main upstroke of lead 2 represents the movement down the *tænia*: the actual summit of the curve, or a point a little past the summit, represents approximately the time at which the excitation wave reaches the region of the coronary sinus and enters the *A-V* node.

#### CONCLUSIONS.

A detailed examination of the electrical axis of the auricle in a case of auricular flutter, shows that this axis revolves during the progress of each auricular cycle through 360 degrees. This revolution of the axis gives us, so we believe, incontestable evidence that the movement of the excitation wave throughout the auricle as a whole is controlled by a re-entrant movement around a circle or an ellipse.

The movement of the axis has been studied in the three chief planes, and from these observations we are able to fix the actual plane of movement in three dimensions in a sufficiently exact manner. The plane approaches to that occupied by the *tænia terminalis* and the mouths of the two cavæ. This evidence and evidence derived by comparing the results from previous experiments on animals, leads us to the belief that the circus movement is occurring around the mouths of the two cavæ.

The curves obtained from this patient by means of the customary clinical leads are of a familiar type: we conclude therefore that circus movement in human flutter is usually around the two cavæ, and that probably this movement is usually, though we do not suggest that it is always, down the *tænia terminalis* and up the left auricle.

## REFERENCES.

- <sup>1</sup> EINTHOVEN, BERGANSIUS and BIJTEL. *Archiv f. d. ges. Physiol.*, 1916, CLXIV, 167.  
<sup>2</sup> LEWIS, FEIL and STROUD. *Heart*, 1918-1920, vii, 191.





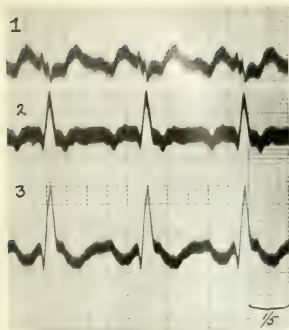


Fig. 8.

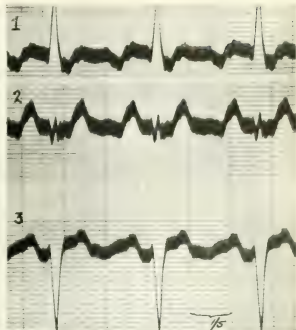


Fig. 9.

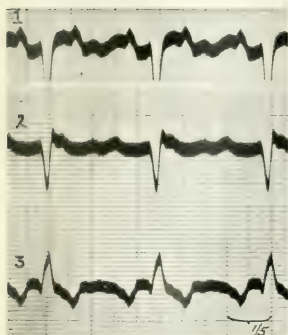


Fig. 10.

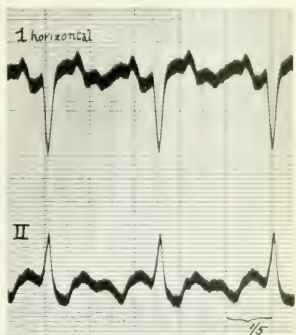


Fig. 11.

Fig. 8. (Record 3, 27 2 21.) *Sagittal plane.* Simultaneous electrocardiograms taken by three leads (1, 2 and 3) from contacts arranged triangularly on the chest wall in the sagittal plane. In this and succeeding figures, 1 centimetre = 1 millivolt.

Fig. 9. (Record 10, 23 2 21.) *Frontal plane.* Simultaneous electrocardiograms by three leads (1, 2 and 3) from contacts arranged triangularly on the chest wall in the frontal plane.

Fig. 10. (Record 3, 30 3 21.) *Horizontal plane.* Simultaneous electrocardiograms by three leads (1, 2 and 3) from contacts arranged triangularly on the chest wall in the horizontal plane.

Fig. 11. Simultaneous electrocardiograms taken by lead I of the horizontal group of leads, and by lead II, the right arm and left leg.





Fig. 12. A photograph of a ring, to indicate as nearly as possible the plane of the circus movement in the auricle of our patient, looking at the patient from in front. The near limb of the ring, in which the movement is a descending one, is thought to represent the tinea terminalis; the far limb of the ring, in which the movement is an ascending one, is thought to represent the wall of the left auricle. Seen from the front the movement is anticlockwise, so it is when viewed from above (direction of arrow *b*); but when viewed from the right of the patient (direction of arrow *a*) it is clockwise.

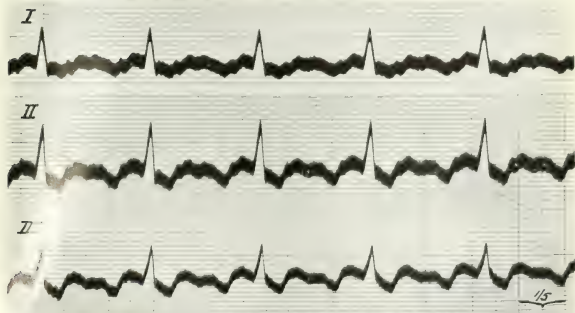


Fig. 13. Simultaneous electrocardiograms taken from the usual three clinical leads *I*, *II* and *III*.



## A DEMONSTRATION OF CIRCUS MOVEMENT IN CLINICAL FIBRILLATION OF THE AURICLES.

By THOMAS LEWIS, A. N. DRURY and C. C. ILIESCU.\*

(*University College Hospital Medical School.*)

IN the preceding article it has been shown that in a case of clinical flutter the electrical axis of the auricle revolves during the progress of each cycle, as is to be expected if flutter of the auricle is controlled by a circular movement of the excitation wave. In the present article similar observations upon the electrical axis in cases of auricular fibrillation are described. The same method has been employed as in the case of flutter: we take three simultaneous curves from the points of a triangle, and utilise in each case the three planes, sagittal, frontal and horizontal.

### *First case.*

S., a pensioner, of 39 years, was discharged from the Army because of breathlessness and easy fatigue, in May, 1916, after serving for twelve months. He has been under observation for chronic fibrillation of the auricle for seven months.

The heart is enlarged, the impulse lying in the 5th space,  $1\frac{1}{2}$  inches beyond the nipple: the ribs move with the heart beat. He has mitral stenosis, evidenced by a full diastolic or early diastolic rumble at the apex.

He presents signs of congestion, becoming cyanosed on lying down and having engorgement of the veins and liver. Of recent months, during the period over which the following observations have been undertaken, his condition has improved, on a régime of rest and digitalis. In the period during which the records were taken he was taking tincture of digitalis in variable doses, usually small doses, sometimes heavy ones.

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\* Working on behalf of the Medical Research Council. A preliminary account of these observations has been published in the Proceedings of the Physiological Society, March 12, 1921.

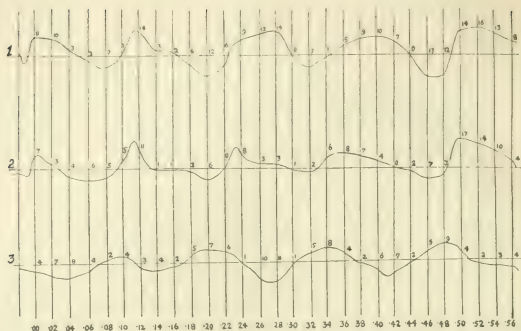
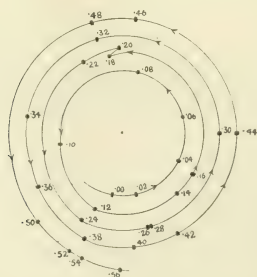


Fig. 1. *Case I. (Record 2, 16 3/21.) Sagittal plane.* The oscillations (*a* to *e*) of Fig. 12 have been enlarged 12.2 diameter and traced. These curves have been measured from appropriate base lines and the measurements in millimetres are written on the three curves at intervals of fiftieths of a second. The chart has been reduced in reproduction. These measurements, after minor correction (Table 1) have been used to calculate the set of the electrical axis at fiftieths of a second intervals, during the progress of the four auricular cycles.



Sagittal plane, Lead I, (membrane to xiphisternum).

Fig. 2. *Case I. (Record 2, 16 3/21.) Sagittal plane.* At the angles, calculated from the last figure, lines have been drawn from a centre point to a spiral line, on which are marked the crossing points of the angle lines, and the appropriate times (Fig. 1) have been written against these points. The angles have been plotted relative to the line of lead I in the sagittal plane, from which the leads were used.

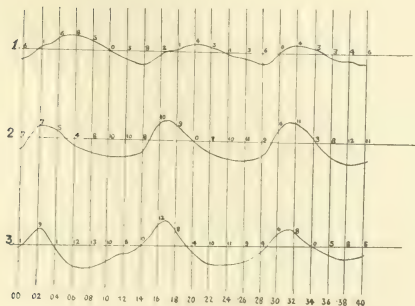


Fig. 3.

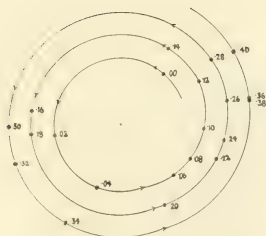


Fig. 4.

Fig. 3. *Case I. (Record 8, 16 3 21.) Sagittal plane.* A chart similarly constructed from oscillations *a*, *b* and *c* of Fig. 14. The original enlargement was to 12.2 diameter. The corresponding table is Table II. The angles are plotted in Fig. 4.

*Sagittal plane.* We have taken simultaneous curves in this plane on six separate occasions over a period of three months: the curves of each group are similar and show consistent relations to each other. The form of curve from any of the three leads, and the relation of the oscillations of the different leads to each other, are not constant from moment to moment; but similar variations have been discovered on each occasion upon which he has been examined.

Fig. 12 is our first illustration. Three ventricular complexes are shown, and between these appear the characteristic curves of the fibrillating auricle. The oscillations are irregular in amplitude, length and form, within certain limits; but, as is usual, the prevailing form is a relatively abrupt upstroke and slower decline. In the curves of leads 1 and 2\* corresponding oscillations are very similar and corresponding points upon them are almost synchronous: the upstrokes, however, are not quite synchronous, they begin earliest, though by a very small fraction of a second in curve 1. In the curve of lead 3 the oscillations are more rounded and their upstrokes are less abrupt: these oscillations begin to rise distinctly earlier than do the rises in curves 1 and 2. Similarly the summits in curve 3 very distinctly precede those of curves 1 and 2. This type of record, as we shall see, is associated with an anticlockwise rotation of the electrical axis in the particular plane used. It is to be observed that the oscillations are not equally distinct over the whole record; particularly is this the case in curve 3, at the end of which the oscillations are diminutive and broken. We have chosen for further analysis four oscillations *a* to *e*, and the chart of these is published in Fig. 1. The measurements are given in Table I and the angles are plotted in Fig. 2. Because we trace the angles over several cycles, the manner of expressing these, hitherto adopted, has been modified. Lines, which are not shown in the figure, are drawn from the centre point at the correct angles to cut a spiral, and the successive fiftieths of a second are written against the spiral at the points of crossing. It will be seen that, throughout the four cycles charted, the electrical axis revolves in an anticlockwise fashion, with the unimportant exception of a slight movement in the reverse direction (between 0.18 and 0.20 of a second). The points on the spiral are not equidistant: neither are they uniformly distributed, but tend to congregate above and below. A similar distribution was seen in our case of flutter, and its significance appears to be that the movement, as it is projected on the sagittal plane, is not circular but somewhat elliptical.

Fig. 14 is a second example of very similar kind. The oscillations are maximal and of almost equal amplitude in all leads in the early phase of the record: in the later phases they are less conspicuous. The oscillations (*a*, *b* and *c*) at the beginning are almost uniform in form and size. In curves

\*The points used in leading off in this and other planes are described precisely in the preceding article (page 344). The curve is labelled in each instance according to the lead from which it was taken.



TABLE I. (*Case I. Record 2, 16.3.21.*)  
(*Sagittal plane.*)

Seconds.	Leads; E.M.F. in millivolts ( $\times 122$ ).			Angle.	E. in millivolts.
	1	2	3		
0.00	11	7	-4	9	0.09
0.02	16	3	-7	-13°	0.08
0.04	3	-4	-8.7	-65°	0.06
0.06	-3	-6.7	-4	-115°	0.06
0.08	-7	-5	2	-166°	0.06
0.10	1	5	4	79°	0.05
0.12	14	11	-3	18°	0.12
0.14	3	-1	-4	-43°	0.03
0.16	2.1*	-1	-2	-60°	0.02
0.18	-6	-2	5.4	169°	0.05
0.20	-12-13	-6	7	177°	0.11
0.22	-6	0	6	150°	0.06
0.24	9	8	-1	24°	0.08
0.26	13	3	-10	-17°	0.11
0.28	14	3	-11	-18°	0.12
0.30	0	-1	-1	-90°	0.09
0.32	-7-8	-2	5	164°	0.07
0.34	-1	6	7	98°	0.06
0.36	5	8.9	4	56°	0.07
0.38	9	7	-2	18°	0.08
0.40	10	4	-6	-7°	0.08
0.42	7	0	-7	-30°	0.07
0.44	0	-2	2	-90°	0.02
0.46	3-12	-7	5	174°	0.10
0.48	-12	-3	9	165°	0.10
0.50	14	17.18	4	42°	0.15
0.52	16	14	2	23°	0.14
0.54	13	10	-3	17°	0.11
0.56	8	4	-4	0°	0.07

\* The figure which is crossed out is that which represents the original measurement; it has been altered to render the fit perfect for purposes of calculation.

TABLE II. (*Case I. Records, 16.3.21.*)(*Sagittal plane.*)

Seconds.	Leads; E.M.F. in millivolts ( $\times 122$ ).			Angle.	E. in millivolts.
	1	2	3		
0.00	-6	-7	-1	-143°	0.06
0.02	1	7	9.6	82°	0.06
0.04	6	5	-1	21°	0.05
0.06	8	-4	-12	-49°	0.10
0.08	5	-8	-13	-66°	0.10
0.10	0	-10	-10	-90°	0.09
0.12	-5	-10	-5	-120°	0.08
0.14	-8	-8	0	-150°	0.08
0.16	-2	10	12	99°	0.10
0.18	1	9	8	84°	0.08
0.20	4	0	-4	-30°	0.04
0.22	3	-7	-10	-72°	0.08
0.24	-1	-10	-11	-85°	0.10
0.26	-3	-11-12	-9	-104°	0.10
0.28	-6	-9-10	-4	-127°	0.08
0.30	0	6	6	90°	0.06
0.32	4	11-12	8	70°	0.10
0.34	3	3	0	30°	0.03
0.36	-3	-8	-5	-112°	0.07
0.38	-4	-12	-8	-110°	0.10
0.40	-6	-11	-5	-123°	0.09

1 and 2 they appear to rise simultaneously: but in curve 3 the rises begin at earlier points: in this lead the rise is at first gradual and then more abrupt. These three oscillations are charted in Fig. 3. It will be observed that, whereas the initial rises of the oscillations begin simultaneously in curves 1 and 2, the oscillations of curve 2 cut the base lines first. The base lines are cut at a still earlier phase by the oscillations in curve 3. The order in which the base lines are crossed is 3, 2 and 1, and this arrangement is always associated with a relatively uniform movement in an

TABLE III. (*Case I. Record 11, 9.3.21.*)  
(*Sagittal plane.*)

Seconds.	Leads; E.M.F. in millivolts ( $\times 102$ ).			Angle.	E. in millivolts.
	1	2	3		
0.00	-11	-7	4	-171°	0.11
0.02	-17	-13	4	163	0.17
0.04	-15	16	1	-147°	0.18
0.06	-11	-15 16	-5	-132°	0.16
0.08	-3	-10	-7	-107°	0.10
0.10	10	0	-10	-30°	0.11
0.12	15	6	9	-7°	0.15
0.14	10	5	-5	0°	0.10
0.16	2	2	4	120°	0.04
0.18	-11	-3	8	165°	0.11
0.20	-14	-6	8	175°	0.14
0.22	14	-8	6	175°	0.14
0.24	-7	-7	0	-150°	0.08
0.26	11	6	5	3°	0.11
0.28	12 13	6	8 7	-3°	0.13
0.30	11	6	5	3°	0.11
0.32	-1	2	3	109°	0.03
0.34	-10	-2	8	161°	0.10
0.36	-11	4	7	171°	0.11
0.38	-7	-5	2	-166°	0.07

anticlockwise direction. The measurements are given in Table II and the angles are plotted in Fig. 4. An uninterrupted anticlockwise movement is shown and, with the exception of a gap to the left and above in the diagram, the distribution of the points is unusually uniform.

In Fig. 15 is a record taken on another day. The plane was approximately sagittal, though it was tilted a little above towards the left shoulder, and, as a consequence, the ventricular curves have altered their forms. In the record the overlap between curves 1 and 2 is first visible, and that between curves 2 and 3 is, as usual, conspicuous. The record is however, unusual in several respects. Of most importance is the direction of the overlaps; whereas in previous figures the rise is delayed in passing from

TABLE IV. (Case I. Record 11, 9/3/21.)

(Sagittal plane.)

Seconds.	Leads: E.M.F. in millivolts ( $\times 102$ ).			Angle.	E. in millivolts.
	1	2	3		
0-00	5	6	1	39°	0-06
0-02	4	1	-3	-16°	0-04
0-04	3	-4	-7	-65°	0-07
0-06	-4	-4	0	-150°	0-05
0-08	2	5	3	67°	0-05
0-10	3	8	5	68°	0-08
0-12	3	3	0	30°	0-03
0-14	5 6	3	-3	0°	0-06
0-16	2	0	-2	-30°	0-02
0-18	3	-2	-5	-53°	0-05
0-20	-1	-4	-3	-104°	0-04
0-22	-9	-6	3	-169°	0-09
0-24	7	9	2	42°	0-09
0-26	4	6	2	49°	0-06
0-28	6	4	-2	11°	0-06
0-30	5	2	-3	-7°	0-05
0-32	6	2	-4	-11°	0-06
0-34	4	-2	-6	-49°	0-06

curve 3 to curve 1, it is now delayed in passing from 1 to 3. Such overlaps are always associated with a *clockwise* movement of the axis. It is also to be observed that the form of curve has altered, more especially in lead 3. The usual type in this lead is an oscillation rising slowly and falling away more abruptly: in the present curve the rise is abrupt and the fall more gradual. This form of record has not been peculiar to the sagittal lead rotated a little towards the left shoulder, for a similar reversal of the movement of the axis has been seen on most of the occasions on which the sagittal plane has been examined in this patient, whether the plane has been precisely sagittal or a little tilted. A second record, Fig. 13, taken on the same day, shows both clockwise and anticlockwise movements. Thus, in the earlier part of this record are three oscillations, *a*, *b* and *c*, in which the rise is obviously latest in curve 3: while in the later phases of the record (*k* and *l* especially) the oscillations of the curve 3 have precedence. The

charted portions of this record are shown in Figs. 5 and 6, the measurements are given in Tables III and IV, and the angles are plotted in the combined diagram, Fig. 7.

It is to be emphasised that the clockwise movement in the sagittal plane is exceptional in this patient, and when it appears is never long maintained: the predominant movement is anticlockwise. The meaning of this occasional and temporary reversal will be discussed at a later stage.

Two other types of record have been obtained from the sagittal plane in this patient. The first is comparatively fleeting, but has been seen on a number of occasions. The oscillations in curves 1 and 2 are similar in form and amplitude, while curve 3 remains practically isoelectric. This phenomenon is shown in Fig. 16, oscillations *a*, *b* and *c*. It is clear that the potentials at any given instant are equal (whether + or — quantities) in curves 1 and 2, from which it is to be deduced that the axis is setting alternately at 30 and —150 degrees. There is no rotatory movement, but a movement up and down one line: but these oscillations, which show the constant set of the axis up and down a single line, are in series with others (namely, *h* and *i*), which speak for the usual anticlockwise movement. The meaning of the change is hardly to be doubted: the explanation is that which has been put forward already by Drury and Ilescu to explain the sudden disappearance of oscillations from a single lead. It is that the plane of the circus movement has altered. If a wave is circulating in or near the sagittal plane, and its movement controls the set of the electrical axes from instant to instant, these axes will show rotation: but if at any time the plane of movement alters, so that it comes to lie at right angles to the sagittal plane then the circular movement will no longer be represented in the sagittal plane: the axis will set up and down one line, although the circular movement continues. Theoretically, to bring about such an alteration, the plane must rotate through 90 degrees, more or less, according to its original inclination to the sagittal plane. Probably the plane becomes rotated by some 45 to 90 degrees. The highest figure at all probable is 135 degrees, but there are reasons for regarding so large a movement as unlikely.

The second unusual type of curve is one in which curve 2 becomes almost isoelectric, while curves 1 and 3 show equal amplitudes, their several phases being opposite in direction. Such records are also to be explained by rotation of the plane of movement, the axes setting up and down a line, having an inclination of —30 degrees and 120 degrees to the line of lead 1. To convert curves of the first type described, in which curve 3 becomes isoelectric, to those of the second type, in which curve 2 becomes isoelectric, would require a rotation of the plane of movement through no less than 60 degrees.

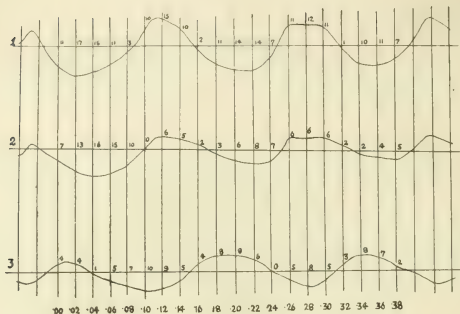


Fig. 5. *Case I.* (Record 11, 9/3/21.) *Sagittal plane.* A chart similarly constructed from oscillations *a* to *c* of Fig. 13. The original enlargement was to 10.2 diameters. The corresponding table is Table III.

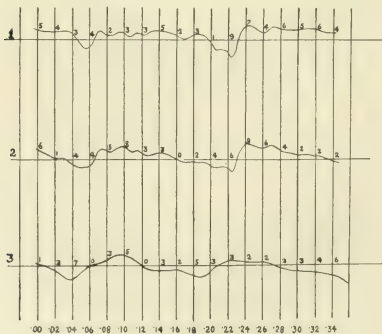


Fig. 6. *Case I.* (Record 11, 9/3, 21.) *Sagittal plane.* A similar chart from oscillations *k* and *l* of Fig. 13. The original enlargement was to 10.2 diameters. Table IV corresponds.

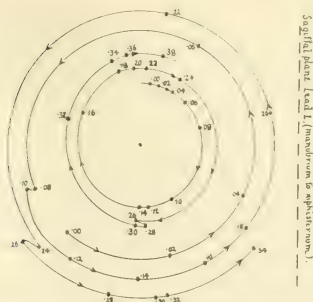


Fig. 7. *Case I. (Record 11, 9.3.21.) Sagittal plane.* This diagram of the angles corresponds to the charts of Figs. 5 and 6. The inner spiral shows a clockwise rotation of the axis corresponding to oscillations *a-c* of Fig. 12; the outer spiral shows an anticlockwise rotation of the axis, corresponding to oscillation *k, l*, of the same record.

We may now return to discuss what happens when the direction of axis rotation changes, as this is projected to a single plane. Such reversal does not necessarily mean that the circus movement, at first moving in one direction through a ring of tissue in the auricle, turns back and retraces its path through the same ring in an opposite direction. There is another and more plausible explanation. A remarkable curve has been published and commented upon by Drury and Hiescu; it is Fig. 10 of their article, and it was taken from the patient which we are now describing. In a record from the chest, taken in the sagittal plane (our lead *I*), the oscillations show an abrupt change of direction. Though we have taken scores of records from this patient, hoping to obtain a similar curve, simultaneously with the companion curve from the other points of the triangle, we have not fully succeeded. Where we have seen a clear reversal of the characteristics of the oscillation (Figs. 13 and 12, *k, l*) already described, the change has been in curve *3*. To explain such reversal in the form of the oscillations it seems to us necessary to suppose a reversed direction so far as that particular lead is concerned. That is possible without the direction of movement becoming reversed in a particular ring of muscle. Suppose that the plane of movement lies at right angles to the plane from which the curves are being taken, and our records speak of this happening in respect of the sagittal plane from time to time, and suppose that the plane of movement rotates about a vertical axis in one direction, the movement will be projected to the plane of the leads as a clockwise movement, while a similar rotation in the opposite direction will result in the movement being projected to the plane of the leads as an anticlockwise movement. Our meaning may be made clearer by means of

Fig. 18, in which a ring is represented in two positions, rotated from a central position to the right or to the left respectively. The movement is around the ring, being up its near limb and down its far limb. According to the angle from which the ring is seen, the movement appears clockwise or anticlockwise. If the ring were placed in the intermediate position, rotation would no longer be visible.

Reversal of the axis rotation as this is calculated in a single plane is susceptible of one of two explanations: either the path travelled is constant, and the direction of movement along it becomes reversed, or the path alters to such a plane that apparent reversal takes place (Fig. 18). A rotation of the plane of not less than 60 degrees to 90 degrees would probably be necessary before both clockwise and anticlockwise movements were well displayed by leads from the same plane. We prefer the last explanation for several reasons. Firstly, such a rotation of the plane of movement would reverse the direction of movement relative to one lead only: reversed direction in a fixed ring of muscle would reverse the direction of movement relative to all three leads. When the change comes, a conspicuous alteration in the type of oscillation has been seen to occur in one lead only, the form being unaltered, or little altered, in the remaining lead or leads. Secondly, reversed movement through a given ring of muscle should be accompanied, we think, by a notable disturbance in the incidence of the oscillations: it is true that in the curve published by Drury and Iliescu this may have happened, but it does not appear to be the rule. Thirdly, if the movement reverses itself in a given ring, it would be expected that this direction of movement would from time to time become stable: actually the change considered is a fleeting one, as though the wave were diverted temporarily soon to return and re-establish itself on the original path. Our final reason is of a theoretical kind: we find it difficult to conceive that a wave may turn backwards on the same path for any considerable distance, for this path would for some time be refractory. This conception was actually discussed by Mines; that the direction may be reversed for a short distance, as when a wave passes around the edge of a refractory barrier of muscle, seems to us conceivable: but our experience of such return is opposed to the view that it happens through anything but relatively short stretches of muscle. Although such evidence as we possess is opposed to reversal in a given ring, and favours the alternate idea that there is a change from one ring to another lying in a somewhat different plane, but having a centre point not far removed from the old one: yet we fully realise that more extensive observations are required from this point of view before a final conclusion can be reached.

*Frontal plane.* A series of records taken in this plane on the same day as Fig. 12, show oscillations of similar amplitude to those already described in so far as the curves of leads 1 and 2 are concerned. In curve 3 the oscillations are for the most part weak, not infrequently disappearing (Fig. 17). When present in curve 3, either in short groups, or over longer



stretches of record, they are seen to precede the corresponding oscillations of curves 1 and 2, indicating an anticlockwise movement of the axis. In one or two records clockwise rotation is indicated during solitary cycles. The prevailing movements in this plane, therefore, are an anticlockwise movement, though not pronounced, and occasional linear movement, up and down an axis inclined at 30 degrees to the horizontal (the inclination being upwards and to the right in the patient's body).

*Horizontal plane.* A series of records, taken from this plane on the same day as those last described, show that in this plane the leads are least favourable. The oscillations are of greatest amplitude in the curve from lead 3 and of relatively small amplitude in those of leads 1 and 2. The oscillations, when distinct in all three curves, are not synchronous: sometimes a clockwise movement of the axis, and on one occasion an anticlockwise movement, is indicated.

*The planes considered together.* The prevailing movement in this patient is anticlockwise in the sagittal plane, less pronouncedly anticlockwise in the frontal plane, and very weakly clockwise in the horizontal plane. Imagine a ring of muscle lying in the sagittal plane, and that movement is up the anterior limb of the ring and down the posterior limb. Let this ring be moved a little so that its anterior limb comes to lie more towards the left in the patient's body and the posterior limb more towards the right: let the ring be tilted also, though very slightly, so that the top of it is carried a little towards the patient's right shoulder, and an approximate idea of the predominant movement as seen in three dimensions is obtained.

### *Second case.*

We have investigated the movements of the auricular electrical axis and have obtained evidence of rotation in four cases of fibrillation of the auricles. Our first case is described in some detail: a briefer description of a second case, to confirm the main observations in our first case, should suffice to illustrate our observations.

M., a pensioner of 24 years, was discharged from the Army because of breathlessness and giddiness on slight effort, after serving for eighteen months. He has been under observation for chronic fibrillation of the auricles for nine months.

The heart is enlarged, the heaving impulse lying in the 6th space, 2 inches beyond the nipple line: the ribs move with the heart beat. He has mitral stenosis, as evidenced by a full diastolic or early diastolic rumble at the impulse. When first seen he was suffering from heart failure with congestion, the liver being engorged. Of recent months his health has much improved under a régime of rest and digitalis therapy. While the following observations were being made, he was taking 15 to 30 minims of digitalis tincture daily.

TABLE V. (*Case 11. Record 9, 5 3 21.*)  
(*Frontal plane.*)

Seconds.	Leads; E.M.F. in millivolts ( $\times 74$ ).			Angle.	E. in millivolts.
	1	2	3		
0-00	7	9 10	3	47°	0-14
0-02	6	6	0	30°	0-09
0-04	0	-3	-3	-90°	0-05
0-06	-2 7	-7 9	-2	-138°	0-13
0-08	-8	-9	1	-144°	0-13
0-10	-8	-8	0	-150°	0-12
0-12	4	6 5	1	41°	0-07
0-14	4	8	4	60°	0-11
0-16	3	7 8	5	68°	0-11
0-18	5 4	4	0	30°	0-06
0-20	2	-2	-4	-60°	0-05
0-22	-5	-8 9	-4	-124°	0-12
0-24	-9	-10 11	-2	-140°	0-16
0-26	-10	-9	1	-155°	0-15
0-28	0	0	0	—	—
0-30	7 6	8	2	44°	0-11
0-32	6	9	3	49°	0-12
0-34	6	8 9	3	49°	0-12
0-36	8	6	-2	16°	0-11
0-38	4	1	-3	-16°	0-06
0-40	-3	-8	-5	-112°	0-11
0-42	-8	-8	0	-150°	0-12
0-44	-7	-5	2	-166°	0-10
0-46	6	8 9	3	49°	0-12
0-48	7	8	1	37°	0-12
0-50	6	7 6	0	30°	0-09
0-52	7	6	-1	22°	0-10
0-54	4	1	-3	-16°	0-06
0-56	-1	-4 5	-5 4	-101°	0-07
0-58	-7	-7	0	-150°	0-11
0-60	-3	0	3	150°	0-05
0-62	7	9 10	3	47°	0-14
0-64	7	8 9	2	42°	0-13

TABLE VI. (*Case II. Record 1, 5321.*)  
(*Frontal plane.*)

Seconds.	Leads; E.M.F. in millivolts (> 74).			Angle.	E. in millivolts.
	1	2	3		
0.00	5	8	3	52°	0.11
0.02	3	7	4	65	0.10
0.04	1	4	3	76°	0.06
0.06	0	1	1	90°	0.02
0.08	-1	-4-5	4	-101°	0.07
0.10	0	-6-7	7	-90°	0.11
0.12	5	0	-5	-30°	0.08
0.14	5	6	1	39°	0.09
0.16	3	7-8	5	68°	0.11
0.18	-1	3	5-4	104°	0.06
0.20	-4	-1	3	164°	0.06
0.22	3	-4	-1	-136°	0.06
0.24	-2	-6	-4	-109°	0.08
0.26	1	-4	-5	-79°	0.07
0.28	4	0	-4	-30°	0.06
0.30	2	4	2	60°	0.05
0.32	-2	6	8	104°	0.11
0.34	-5	4	9	124°	0.12
0.36	-6	2	8	136°	0.11
0.38	-7-8	-2	6	164°	0.11
0.40	-7-8	-7	1	-157°	0.12
0.42	-4	-4	0	-150°	0.06
0.44	1	0	-1	-30°	0.02
0.46	8	8	0	30°	0.12
0.48	2	4	2	60°	0.05

*Frontal plane.* Leads in this plane have been used on six separate occasions, extending over a period of one month. The curves have been remarkably uniform in type, exceptional records being taken on a few occasions. The prevailing type of record is shown in Fig. 19. The oscillations are very conspicuous in the curves of leads 1 and 2, less

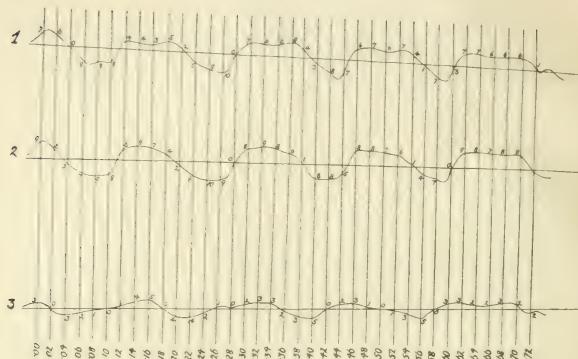


Fig. 8.



Fig. 9.

Fig. 8. Case 11. (Record 9, 5321.) Frontal plane. Oscillations *a* to *c* of Fig. 19 are charted. The original enlargement was to 7.4 diameter. Table V corresponds.

Fig. 9. Case 11. (Record 9, 5321.) Frontal plane. The diagram of angles corresponds to the chart of Fig. 8. The angles have been plotted relative to the line of lead *I* of the frontal plane.

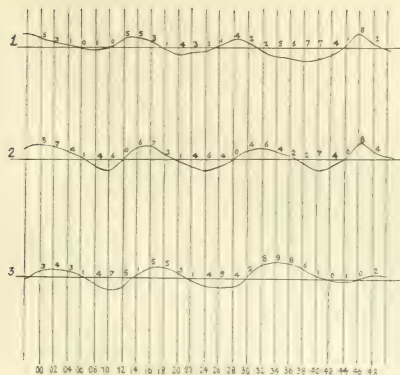


Fig. 10.

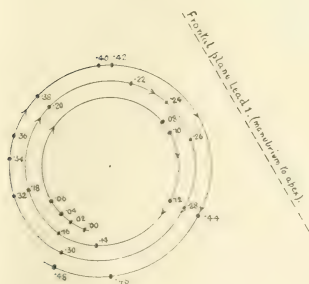


Fig. 11.

Fig. 10. *Case 11. (Record 1, 5 3 21.) Frontal plane.* A chart of oscillations *a* to *d* of Fig. 20. The original enlargement was to 7.4 diameter. Table VI corresponds. The angles have been plotted in Fig. 11.

conspicuous in those of lead 3. The rises occur simultaneously in curves 1 and 2, but both are preceded by the rise in curve 3. An anticlockwise movement is thereby indicated. The oscillations *a* to *c* are charted in Fig. 8: the measurements are given in Table V and the angles are plotted in Fig. 9. The movement of the axis for four cycles is uniformly anticlockwise, with the exception of two insignificant movements in a reverse direction (at 0.12 to 0.16 and at 0.30 to 0.32).

In very occasional records a clockwise movement was exhibited in this plane, and is exemplified by Fig. 20. The oscillations are now almost equally conspicuous in the three leads. Overlap occurs between curves 1 and 2, and also between curves 2 and 3. The rise comes first in curve 1 and latest in curve 3, as is usual when the movement is clockwise. Oscillations *a* to *d* of this record are charted in Fig. 10, the measurements are given in Table VI and the angles are plotted in Fig. 11. For three full cycles a remarkably uniform clockwise rotation is to be seen.

In the same record linear movement of the axis is displayed, oscillations (*f*, *k*, and *l*) of equal amplitude and form appearing in curves 1 and 2, while curve 3 shows little or no trace of oscillation. A more pronounced example of the last type of record is shown in Fig. 21. In this, six oscillations of equal form and amplitude appear in curves 1 and 2, while curve 3 is almost stationary.

Thus, the curves taken from the frontal plane in this patient show similar manifestations to those taken from the sagittal plane in the first patient. The bulk of the records exhibit an anticlockwise rotation: that is the predominant movement: occasionally a clockwise movement is exhibited, occasionally the axis sets up and down one line.

*Sagittal plane.* Curves from this plane have been taken on three occasions. The oscillations in this plane are conspicuous, especially in the curves of leads 1 and 3, while in that of lead 2 they are diminutive and sometimes absent. The directions are reversed in curves 1 and 3, but alike and for the most part synchronous in curves 1 and 2. Very occasionally overlap is seen between curves 1 and 2, indicating, for a few cycles only, either clockwise or anticlockwise rotation.

*Horizontal plane.* Curves from leads in this plane have been taken on two occasions. Small oscillations appear in the curves of all three leads from time to time, but they are never conspicuous. They may appear synchronously in all three curves and may then have similar directions: in other portions of the records they are synchronous, but reversed in direction in curves 1 and 3. Occasional overlap is seen, indicating either a clockwise or anticlockwise movement.

*Summary of chief observations and conclusions.*

The observations which we have now recorded seem to us to point conclusively to the nature of auricular fibrillation. A study of the movements of the electrical axis or the auricle confirms in a striking manner the conclusion which has been drawn from experiments on animals, namely, that in fibrillation a single circulating wave controls the beating of the auricles. But this central or circulating wave does not run the constant course which it pursues in flutter: there is very suggestive evidence that the plane of movement alters from time to time: the movement as projected to a single plane may actually show reversal. We are opposed to the view that such reversal indicates flow in a contrary direction through a single circular path: and attribute it to swing of the plane of movement through some 60 degrees or 90 degrees, perhaps more, whereby the direction of movement, as projected to a single plane, is reversed. The swing of the plane we attribute to the excitation wave temporarily entering and travelling through a new channel for a few cycles, shortly to revert to its original channel.

The records taken from a given patient from time to time show considerable uniformity for particular leads and planes. It is true that there is variation, but in a given lead one type of curve predominates and in a given plane one type of movement of the electrical axis predominates. Such variations from these types as are seen are repeated from time to time. The mechanism in fibrillation of the auricles, though it is a mechanism which varies from cycle to cycle and from one record to the next, is constant with its own peculiar variations for any given patient. In such patients there appears to be a definite channel, for which the central excitation wave shows a predilection: sometimes, perhaps, it is forced out of this channel, but if this happens the wave soon returns to its old path, repeating its old course and in the original direction.

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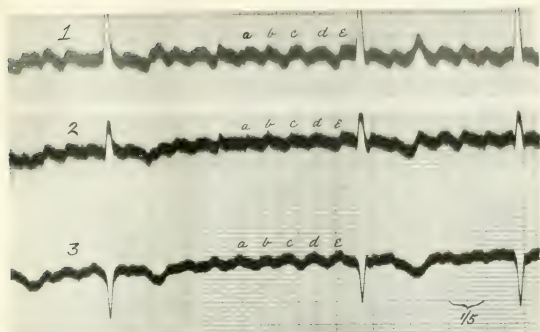


Fig. 12. *Case 1. (Record 2, 16321.) Sagittal plane.* Simultaneous electrocardiograms by leads 1, 2 and 3. The record from which Fig. 4 has been constructed. The time in this and succeeding records is in fifths and tenths of a second. Ordinates 1 centimetric 1 millivolt.

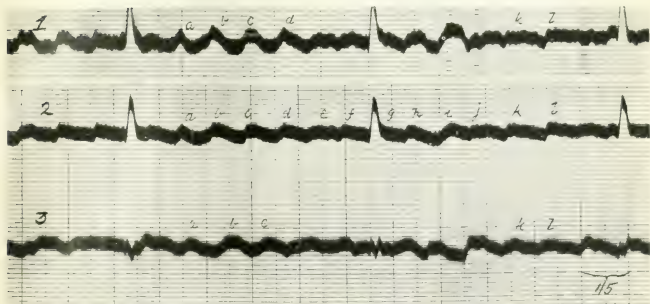


Fig. 13. *Case 1. (Record 11, 9321.) Sagittal plane.* Simultaneous electrocardiograms by leads 1, 2 and 3. The record from which Figs. 5 and 6 have been constructed.





Fig. 14. Case 1. (Record 8, 16.3.21.) *Sagittal plane.* Similar curves used in constructing Fig. 3.

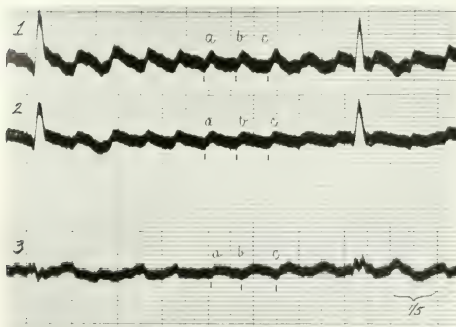


Fig. 15. Case 1. (Record 6, 9.3.21.) *Sagittal plane.* Similar curves showing that the oscillations (a, b and c) of curve 1 rise first, of curve 2 rise second, and of curve 3 rise last.



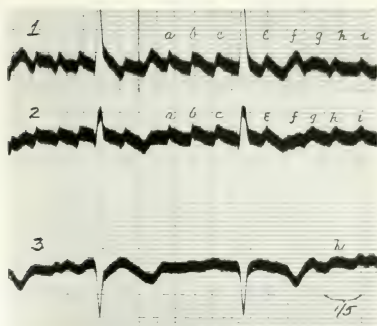


FIG. 16. Case 1. Record 6, 16.3.21. Sagittal plane. Similar curves showing simultaneous and almost equal oscillations in curves 1 and 2, while curve 3 remains almost isoelectric.

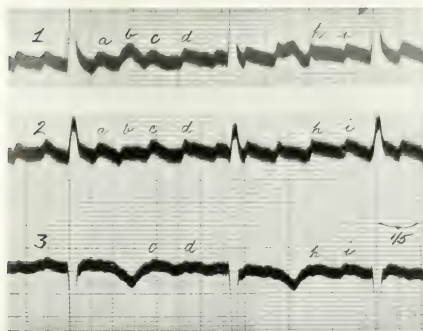


FIG. 17. Case 1. Record 3, 9.3.21. Frontal plane. Similar curves showing simultaneous and almost equal oscillations a-e in curves 1 and 2, while curve 3 is almost isoelectric. At i, the oscillation rises first in curve 3.





Fig. 18. A photograph of a ring deviated a little to the right and a little to the left, to show how these deviations expose anticlockwise and clockwise movements.

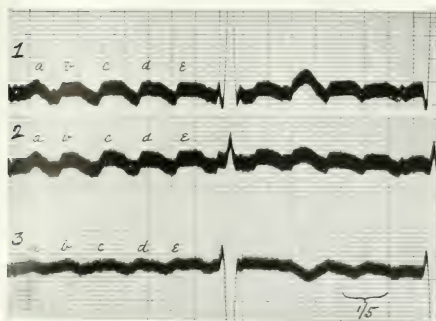


Fig. 19. Case 11. (Record 9, 5321.) Frontal plane. This record has been used in constructing Fig. 8.





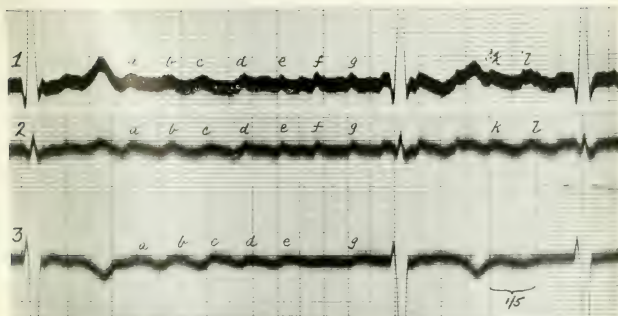


FIG. 20. Case 11. (Record 11, 5321.) Frontal plane. This record has been used in constructing the chart of oscillations *a* to *d* (Fig. 10). The relation of these oscillations in the three curves shows a clockwise movement of the axis. Later in the curve the oscillations of curve 1 and 2 are synchronous, and are of equal amplitude, while curve 3 shows little or no trace of them.

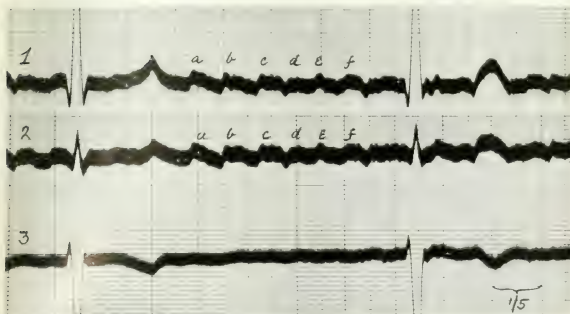


FIG. 24. Case 11. (Record 11, 5321.) Frontal plane. Curves from three leads, showing simultaneous oscillations of equal amplitude in curves 1 and 2, while curve 3 is almost isoelectric.



# HEART.

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## A CASE SHOWING BUNDLE BRANCH BLOCK WITH EXTRA-SYSTOLES ORIGINATING IN THE VENTRICULAR SEPTUM.

By ALBION WALTER HEWLETT.

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THE type of ventricular complex, usually attributed to defective conduction in a main branch of the His-bundle, is characterised (1) by a prolongation of *Q.R.S.*, which often shows a large amplitude in leads *I* and *III* and a notching in these leads, and (2) by a T, which in leads *I* and *III* is directed in the opposite direction from the main *Q.R.S.* deflection, and which is often of large amplitude. Such complexes, when of supraventricular origin, have been interpreted as bundle branch block (1), mainly because analogous changes occur when a primary branch of the His-bundle is cut or compressed in animals. The post-mortem study of hearts from patients who showed such aberrant complexes during life has only partly confirmed this interpretation: for while in some instances the assumed lesion in one of the primary subdivisions of the His-bundle has been found, in others it has not been demonstrated. Such failures do not necessarily invalidate the above hypothesis, since it is known that no anatomical cause may be found for an A-V block that had been demonstrated during life. Oppenheimer and Rothschild (2) have offered a different explanation for aberrant ventricular complexes which resemble those that we are considering. On pathological examination they found lesions that involved the finer subdivisions of the His-bundle. Hence they proposed the designation "arborization block." Wilson and Herrmann (3) have shown that complexes similar to those described by Oppenheimer and Rothschild may result in animals from delayed conduction in one branch of the His-bundle, and they (3) have reported case records where this seemed the probable interpretation in man. In any event it is certain that transitions occur between the complexes usually regarded as typical of bundle branch block and the complexes described by Oppenheimer and Rothschild.

In discussing this question, Wilson and Herrmann (3) pointed out that extrasystoles originating in the ventricular septum might serve to differentiate a bundle branch block from an arborization block. If the block were located in a primary branch of the His-bundle, an extrasystole which started in the septum might enter the Purkinje system of the abnormal

side below the block at about the same time that it entered the Purkinje system of the normal side. Thus the wave of excitation would reach the two ventricles more or less simultaneously and the resulting ventricular complex would show a relatively normal form. If, however, the block were located in the arborization of the Purkinje fibres, then any extrasystole would presumably encounter this block and the form of extrasystoles would not be likely to be more normal than the form of complexes of supraventricular origin. In a case showing a disturbance of conduction to the right ventricle, Wilson and Herrmann pictured an extrasystole which was more nearly normal than the regular beats of supraventricular origin. Concerning this they make the following comment:—"Assuming that the ventricular extrasystole (cycle A2, Fig. 19) was due to a single stimulus and not to two stimuli, one arising in each ventricle, which occurred simultaneously, then delayed conduction through the right branch of the His bundle was probably present in the heart from which this curve was obtained." The following case lends support to the argument of Wilson and Herrmann.

The patient, 64 years old, entered Lane Hospital on April 12, 1921, complaining of shortness of breath and retention of urine. He had noticed occasional palpitation for thirty years, and his pulse had been somewhat intermittent for years. For several years he had noticed shortness of breath on exertion, some swelling of the feet, and evening cough. For two or three years also he had had nocturia, difficulty in starting the urine, and dribbling. Two weeks before entering the hospital he had been unable to void his urine, and he had since been catheterized several times. Simultaneously his shortness of breath became more troublesome. He had not voided for three days previous to coming to the hospital.

Examination showed a badly prostrated old man. The heart was moderately enlarged with a systolic murmur at the apex and occasional extrasystoles. The marked abdominal distension was relieved by withdrawing 100 oz. of urine by catheter. Despite the poor circulation, a suprapubic cystotomy was performed on April 29, and a suprapubic prostatectomy on May 1. The patient made a good operative recovery. Subsequent examinations, in June and July, 1921, showed marked improvement in his general health. Some shortness of breath still persisted and his heart was still moderately enlarged.

Electrocardiograms were taken on April 15, and again on April 22, previous to the operations (Fig. 1). In these the regular beats of supraventricular origin showed all the characteristics ascribed to a right bundle branch block except that the waves were not of remarkably large amplitude. *Q, R, S*, had a duration of 0.12-0.14 second, and showed a tendency to bifurcation in leads *I* and *III*. In these leads *T* was directed in the opposite direction from *Q, R, S*, and the ventricular complex had a diphasic form.

Rather frequent ventricular extrasystoles were recorded. In leads *I* and *II* their form resembled that of normal ventricular complexes, *Q.R.S.* being approximately 0.10 second in duration. In lead *III* the extrasystoles were of small amplitude, and the interference with P frequently obscured their form. Nevertheless *Q.R.S.* appeared to be of brief duration in this lead. In each lead T of the extrasystoles was directed in the opposite direction from T of the regular rhythm.

For these extrasystoles of relatively normal form, in a case showing evidence of disturbed conduction in the right ventricle, we are unable to offer any explanation other than that they originated in the interventricular septum. In our case the considerable number of these extrasystoles, all of the same form, disposes, we believe, of the possibility that each was due to two stimuli arising simultaneously, one in each ventricle. We assume that in these extrasystoles the excitation wave reached the conducting system of the right ventricle below the block at about the same time that it reached the conducting system of the left ventricle. Manifestly this could have occurred if the block had been located in the upper portion of the right branch of the His bundle. This branch gives off only minor ramifications during its passage along the surface of the ventricular septum. The main bundle of fibres leaves the septum almost intact to terminate in the papillary muscles. Animal experiments indicate that a block in such small ramifications as may leave the main bundle of fibres during its passage along the septum could not have caused the marked change in the ventricular complex which was present in this patient. Furthermore, an arborization block, located beyond the point where the branch left the septum, would have influenced the form of septal extrasystoles in much the same way as it influenced the form of the complexes of the regular rhythm. We are led to conclude, therefore, in accord with the reasoning of Wilson and Herrmann, that the relatively normal form of these extrasystoles indicated a block in the right branch of the His bundle rather than in its finer arborizations.

Electrocardiograms (Fig. 2) taken from this patient in June and July, 1921, showed a disappearance of the more striking signs of bundle branch block. The duration of *Q.R.S.* was 0.08 second or less, and only the slightly negative T in lead *I* indicated that we had to do with any change other than a left ventricular preponderance. It is difficult to assign an exact cause for the bundle branch block in this case. Previous to the operation the patient's general condition was poor. The urine contained large numbers of pus cells, but there was no fever and no leucocytosis. The phthalein output was somewhat reduced (25 per cent.) and the blood urea was somewhat increased (65 mg. urea per 100 c.c. of blood). Up to the time the first record was taken no medication had been given save moderate doses of hexamethylenamin and acid sodium phosphate. Presumably the general depression or intoxication incident to urinary retention had caused a bundle branch block in an already damaged heart.

## CONCLUSIONS.

1. A case is reported in which the electrocardiogram showed the changes usually attributed to a block in the right branch of the His-bundle. Frequent extrasystoles were recorded whose form was more nearly normal than the form of the regular beats of supraventricular origin.

2. These extrasystoles probably originated in the interventricular septum.

3. Their presence supports the interpretation of a bundle branch block rather than an arborization block.

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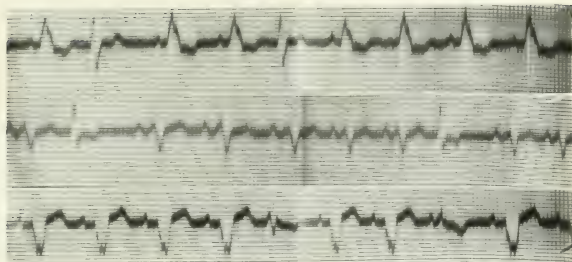


FIG. 1. Records taken previous to operation. Ventricular complexes indicate a block in the right branch of the His bundle. Frequent ventricular extrasystoles of relatively normal form.

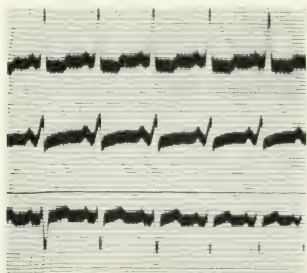


FIG. 2. Taken about one month after operation. The signs of bundle branch block have largely disappeared. In both figures the leads were I, II and III from above downwards, and the time-marker is in twenty-fifths of a second.





## OBSERVATIONS ON THE CIRCULATION AND RESPIRATION IN A CASE OF PAROXYSMAL TACHYCARDIA.

By J. BARCROFT, A. V. BOCK and F. J. ROUGHTON.

(*From the Physiological Laboratory, Cambridge.*)

THE research described below consists of an inquiry in the circulatory condition existing in a state of paroxysmal tachycardia. It has been found possible to measure the quantity of blood passing through the chest per minute: combining the minute volume with the pulse the systolic output is obtained. These quantities were the principal object of our research. Incidentally, however, determinations of the oxygen concentrations of the arterial blood and venous blood have been made and some light is shed on the effect of rapid and shallow respiration on the oxygen content of the arterial blood.

*Clinical history.* F. J. R., a University student of 22 years, has been under observation from October 26th, 1920, to May 8th, 1921. The family and past history are unimportant. He has not had rheumatic fever, diphtheria, scarlet fever, or tonsillitis. His general condition is very good.

The history of the present illness is one of attacks of shortness of breath and palpitation since the age of 11. The original attack came on suddenly after a game of tennis, lasted about one hour, and although alarming in nature, had no serious effect. The next attack followed six months later, also lasting one hour: three other attacks then occurred within a fortnight, none persisting more than two hours. A year passed with no recurrence of the condition, but from that time until April 6th, 1921, there has been a succession of attacks four to eight weeks apart, usually lasting 10-12 hours, but at least one is recorded of 15 hours' duration. These attacks occurred more frequently in winter than in summer. From April 6th, 1921, to May 8th, 1921, six attacks have occurred, none of less than eight hours and the longest lasting twelve hours.

The attacks have an abrupt onset and sudden termination. They are characterised chiefly by shortness of breath, abnormal heart action, cyanosis, gastric disturbance, sweating, and weakness.

The shortness of breath is described as a sensation of "fighting for breath." The patient is unable to take a deep breath without great effort which is most unpleasant if attempted. The inability to get air is associated with the abnormal heart action rather than with a sense of restriction of chest or abdominal movements. He has observed that the rate of breathing is greatly increased.

The rapid "thumping" action of the heart persists throughout the attack, beginning and ending instantaneously. The sensation produced is one of irregularity and uncertainty, which doubtless accounts for a somewhat anxious facies during the course of the syndrome. The patient describes the "amplitude of the beats" as being less in later attacks than formerly.

Cyanosis was pronounced in the early short attacks, but appears not to be a feature of the condition at present. When observed in recent attacks the mucus membranes of the lips were redder than usual and the face appeared generally red and suffused. The hands which normally are blue and cold, show an accentuation of this state during an attack. No note has been made as to cyanosis towards the end of a long attack.

Gastric distress has been a prominent feature of all the later attacks. Nausea begins 4-5 hours after the onset, and is then associated with retching. Vomiting usually stops the attack, particularly if the regurgitation is not forced.

In the first attacks excessive sweating occurred, diminishing in the later ones to about the normal. The later attacks as a whole begin more gently, and there is no great change in the patient's condition for several hours, after which he feels sick and faint and moves about only with great effort. There is no cough. Upon cessation of the attacks, the patient feels in normal condition within an hour.

*Physical examination.* The patient is a well developed athletic young man. There is nothing remarkable in the physical examination. He has good colour, except for blueness of the hands, which are cold and moist. The finger nails are not blue. The heart apex is in the 5th space in the nipple line 11.5 cm. from the mid-sternal line. The sounds are regular, of good quality. There is a soft short systolic murmur localized at the sternal border in the second left intercostal space. The systolic blood pressure is 120 mm. and the diastolic 68-70 mm. of Hg.. The abdominal viscera are not palpable and there is no œdema.

During an attack the face appears anxious and the colour is as noted above. The respiratory rate varies in different attacks from 28 to 34. Resonance of the chest is normal and there are no rales in the lungs. The vital capacity is 1,600 c.c., as compared with his normal of 4,000 c.c.. The heart action is turbulent and can be counted without instrumental means only with great difficulty. A polygraph tracing taken during an attack on October 26th, 1920, shows a rate of 204 per minute. The apex of the heart does not move outward a measurable distance from its normal position. The systolic blood pressure falls from 120 to 100 mm., and the diastolic pressure rises from 68-70 to 80 mm. of Hg.. The liver is not palpable and there is no cedema of the legs.

Vagal pressure has failed to stop the attacks.

A sample of venous blood taken from an arm vein without stasis, 8 hours after the onset of an attack, had an oxygen content of 5.67 vol. per cent., and an oxygen capacity of 18.9 vol. per cent., a saturation of 30 per cent..

The method of determining the minute volume was that described by Barcroft and Roughton\* at the meeting of the Physiological Society in July, 1920. Briefly it consists in taking one deep respiration followed by three or four normal respirations from a bag which contains nitrogen, and then exhaling a sample of alveolar air, the partial pressure of which is estimated in a Haldane gas analysis apparatus. The partial pressure so observed, if laid off on the oxygen dissociation curve, gives the oxygen content of 1 c.c. of mixed venous blood.

That of the arterial blood may be found by the analysis of a sample of blood obtained by direct arterial puncture in the case of patients; in normal cases it may be assumed to be 95 per cent. of the total oxygen capacity. If the oxygen content of the arterial blood be called  $A$ , that of the venous blood,  $V$ , and the total oxygen used by the subject per minute,  $O$ , the "minute volume" of blood  $= \frac{O}{A-V}$ .  $O$  is determined by collecting a five minute sample of expired air in a Douglas bag and measuring its volume and oxygen content.

Of the other measurements made in the course of their research the percentage saturations of the blood arterial and venous (from the arm) were estimated with the differential blood gas apparatus. The blood pressure was taken with a Tyco's instrument.

Unfortunately it was not possible to make a complete series of determinations in any one attack. Different points were studied in different attacks. The minute volume was measured in two attacks and twice when there was no attack in progress. The first of these was just after attack had passed off, the second was under apparently quite normal circumstances.

\* Now in the Press, *Journ. of Physiol.*, Vol. LV.

The following are the data concerned with the minute volume.

	DURING ATTACK.	CONTROL.	
		One hour after attack.	Normal.
Date .. .. .	4/4/21	8/4/21	4/4/21
Pulse rate .. .. .	175	198	82
Oxygen absorbed per minute ..	290 c.c.	232 c.c.	456 c.c.
Oxygen content of arterial blood ..	(95)*	96.8	(95)*
Oxygen pressure in mixed venous blood .. .. .	27 mm.	28.7	36.8
Percentage saturation .. .. .	38	42	57
Minute volume .. .. .	2.8 litres	2.5 litres	6.1 litres
Output of heart per beat .. .. .	16.5 c.c.	12.9 c.c.	75 c.c.

\* Assumed.

† Mean of 8 determinations vary between 36.0 and 32.5 on the 15th of November, 1920.

The above table shows :—

(1) That the oxygen pressure in the mixed venous blood is much lower than is either normally the case or than it was after the attack had passed off on the 4th of April, 1921.

(2) The approximate oxygen contents of the mixed venous blood, obtained by the application of the above pressure to an average dissociation curve, gave the following results :—

	DURING ATTACK.		CONTROL.	
Date .. .. .	4.4.21	8.4.21	4.4.21	13.4.21
Pressure of oxygen in mixed venous blood .. .. .	27 mm.	28.7 mm.	36.8 mm.	35.1 mm.
Percentage saturation of blood with oxygen .. .. .	38	42	57	54.3
Actual oxygen content of 1 c.c. of venous blood .. .. .	0.065	0.0715	0.0975	0.092

One other observation is perhaps worth recording. We correlated the depth of respiration with the percentage saturation of the arterial blood with the following result :—

	Total ventilation*	No. of respirations per minute.	Volume of each respiration.	Percentage saturation of arterial blood.
During attack .. .. .	7.12 litres per min.	28	254 c.c.	96.8
Normal .. .. .	9.00	16	563 c.c.	(95)

\* At 37° c. saturated with aqueous vapour.

The determinations previously described fail to show any lowering of the percentage saturation from the normal as the result of the degree of shallow respiration which was observed in the attack.

During the attack on the 8th of April, 1921, we made an attempt to follow up the high degree of unsaturation of the mixed venous blood. Was it due to want of oxygen in the arterial blood or solely to slow circulation? Samples of the blood from the radial artery and from the basilic vein were therefore withdrawn by direct puncture (for which we have to thank Dr. Frazer, Head of the Medical Unit at St. Bartholomew's Hospital). The arterial blood was saturated up to the level of normal arterial blood, and indeed rather above it (96.8 p.c.). The blood from the basilic vein was but 11 p.c. saturated. The blood from the basilar vein is therefore much less saturated with oxygen than even the mixed venous blood at the same time. It is clear, therefore, not only that the minute volume is reduced to less than half the normal during the attack, but that the brunt of this reduction is taken up by the skin. Quite extreme measures are necessary in normal persons to obtain venous blood of this degree of unsaturation. One of us obtained it on the top of Monte Rosa<sup>1</sup>: it has been recorded also by Meakins and Davies<sup>6</sup> and also by Barcroft and Nagahashi<sup>2</sup>. In Meakins and Davies' case by exposure to cold water, and Barcroft and Nagahashi by exposure of the arm for 15 minutes in the cold storage room.

An interesting point in the two attacks recorded above was the fall in the total oxygen consumption. During the second attack it was as low as 232 c.c. per minute. It is fair, however, to say that in previous attack, during the course of which we made some preliminary determinations, the oxygen consumption was normal. The lowering, therefore, may not take place throughout the whole attack.

Dividing anoxæmia's into three types (3) (the anoxic in which there is an abnormal degree of unsaturation in the arterial blood, the anæmic in which there is too little hæmoglobin per c.c. of blood, and the stagnant or ischæmic, in which there is too slow a circulation) paroxysmal tachycardia presents a clear case of the third type. It is interesting to find that this type may be pushed so far in the human body as to actually cause reduction in the quantity of oxygen used, *i.e.*, a crippling of the metabolism. The same result was found experimentally in cats by Doi<sup>4</sup> who produced the ischæmic type of anoxæmia by bleeding.

The dissociation curve for Roughton's blood is, of course, necessary for the calculation of the minute volume. It is worth recording, though the significance of the observation is not at present clear, that the value of  $K$  was lower than that recorded for any normal person. The value was determined on two occasions giving 0.00014 and 0.00016 respectively, the lowest normal limit being regarded as 0.00025.

It is not possible to carry the research further, for the interesting reason that it seemed to be deleterious to the patient. The strain on the system of making the determination of the minute volume in one case brought on an attack.

## CONCLUSION.

1. In two attacks of paroxysmal tachycardia in which the pulse was upwards of 200 the minute—volume sank from 5.6-1 litres to 2.8-2.1 litres per minute, or roughly to a half to a third of the normal value.

2. The degree of ischaemia was particularly marked in the skin, as shown by analysis of the blood from the basilar vein.

3. There was no reduction in the saturation of the arterial blood, but if anything a rise.

4. The depth of respiration was reduced to nearly half the normal whilst the rate was about doubled.

5. The systolic output 77.5 to 12.9 c.c.

6. The total oxygen consumption of the body was also considerably lowered during two of the attacks.

We should like to express our thanks to Dr. Fraser for his assistance in performing the punctures, to Dr. Adrian and Dr. Forbes for the electrocardiographic records, to the Medical Research Council and the Proctor Fund of Harvard University, out of whose grants much of the apparatus used was purchased.

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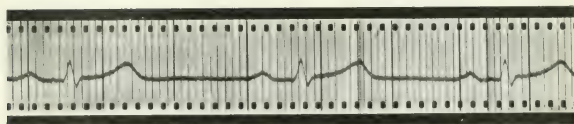


FIG. 1. Electrocardiogram by lead *II*, showing the normal length which prevails between the attacks.

Time marker = 0.29 sec. between thick lines.

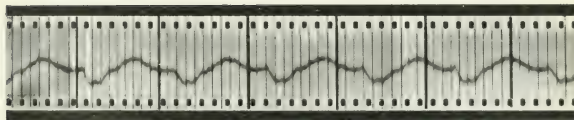


FIG. 2. Electrocardiogram by lead *II*, showing the mechanism during the attack of the 18th of July. The curve consists of ventricular complexes similar to those seen when the beats arise in the left ventricle.

Time marker = 0.27 sec. between thick lines.





## THE SPREAD OF THE EXCITATION WAVE RELATED TO THE STANDARD ELECTROCARDIOGRAM IN THE DOG'S HEART.\*

By A. M. WEDD and W. D. STROUD,

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IN a series of researches which appeared in 1914 and succeeding years, Lewis and his co-workers<sup>1, 2, 3</sup> have recorded extensive observations on the spread of the excitatory process in the heart of the dog. With methods based on the fact that relative negativity is indicated by a deflection in a known direction of the string of the galvanometer, using both direct heart leads and the standard lead *II* of the electrocardiogram, they traced and charted the passage of the excitation wave over the surface of the heart, and as far as possible, the endocardial lining, timing the arrival of the wave at the various places observed with reference to fixed zero points. It has seemed desirable to supplement that work by illustrating in further detail the time relations of the readings taken for the arrival of the excitation wave at various points of the muscle to the standard electrocardiogram (lead *II*) as this was recorded in the same dog's heart. This is possible by re-measuring the original plates.

In the auricle the earliest sign of activity indicated by relative negativity occurs at the sinus node. According to the researches referred to, the spread from the node is radial and at an approximately uniform rate of conduction throughout the auricle. The wave travels from the node by the tania terminalis to the inferior cava and by the inter-auricular band to the base and finally to the tip of the left appendix, which is usually the latest point to be activated. The activity of the sinus node is invariably registered before the beginning of *P*. That of the mid-caval region and the inter-auricular band occurs a few thousandths of a second after the beginning of *P*. The times of activation of the superior and inferior venae cavae, the septum, right appendix and body of the right auricle are seen to occupy points on the upstroke of *P*, varying slightly in different experiments. The activation of the left pulmonary veins and of the coronary sinus occurs well toward or at the summit, while the time for the left appendix is at the summit or on

\* Work undertaken on behalf of the Medical Research Council.

the plateau of *P*. The actual position with reference to *P* of the several points of the auricle investigated is seen in Figs. 1 to 4, which have been selected as typical of the six auricles examined. In the construction of these diagrams the electrocardiograms of lead *II* have been taken from plates that had been measured in the original experiments, and these have been charted to scale by measuring by means of the comparator the points of intersection of the waves and the millimetre horizontal rulings on the plates.

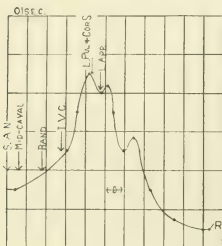


Fig. 1.

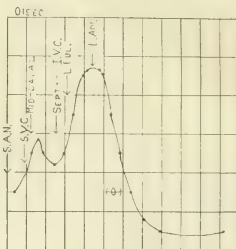


Fig. 2.

Fig. 1. Dog FQ.\* Auricle. Abscissa, 0.01 sec.. Ordinates, 0.1 millivolt. Key to abbreviations for auricle:

S. A. N. Sino-auricular node.  
S. V. C. Superior vena cava  
L. APP. Left appendix.  
L. PUL. Left pulmonary veins.  
COR. SIN. Coronary sinus.

I. V. C. Inferior vena cava.  
R. A. U. R. Body of right auricle.  
R. APP. Right appendix.  
R. P. U. L. Right pulmonary veins.

Fig. 2. Dog FV. Auricle. Abscissa, 0.01 sec.. Ordinates, 0.1 millivolt.

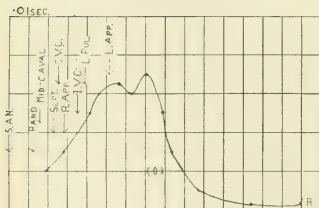


Fig. 3.

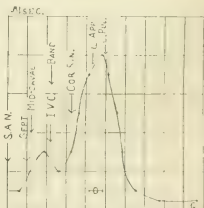


Fig. 4.

Fig. 3. Dog FO. Auricle. Abscissa, 0.01 sec.. Ordinates, 0.1 millivolt.

Fig. 4. Dog FR. Auricle. Abscissa, 0.01 sec.. Ordinates, 0.01 millivolt.

\* The letters refer to the original dogs.

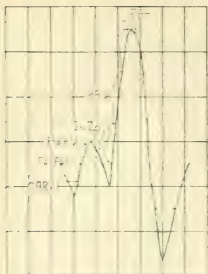


Fig. 5.

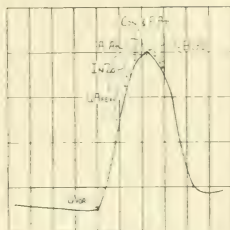


Fig. 6.

Fig. 5. *Fig. 6*. Right surface of ventricle (Fig. 6 of reference 2). Abscissa, 0.01 sec. Ordinate, 0.2 millivolts. Key to abbreviations for ventricle:—

- P.M.R.V. Papillary muscle of right ventricle.
- T.A.R.V. Trabeculated area, right ventricle.
- A.P.R.V. Apex of right ventricle.
- L.V.O.R. Vortex of left ventricle.
- I.N.Z.O. Intermediate zone (R.S., right surface; L.S., left surface).
- A.A.T. Anterior attachments, left ventricle.
- P.A.T. Posterior attachments, left ventricle.
- B.R.V. Base of right ventricle.
- B.L.V. Base of left ventricle.

Fig. 6. *Fig. 9*. Left surface of ventricle (Fig. 9 of reference 2). Abscissa, 0.01 sec. Ordinate, 0.2 millivolts.

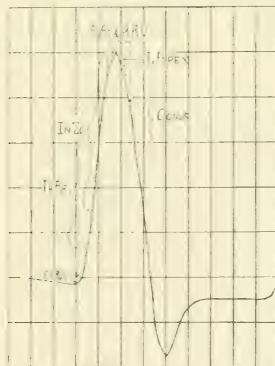


Fig. 7. *Fig. 21*. Ventral surface of ventricle (Fig. 21 of reference 2). Abscissa, 0.01 sec. Ordinate, 0.2 millivolts.

The times of arrival of the excitation wave at the points observed, as given in the original papers, were then marked against these curves in chronological order. These time intervals published by Lewis refer to a zero point which for the auricle is the initial activity of the sino-auricular node, and for the ventricle the beginning of the upstroke of *R* in the standard lead *II*. It is emphasised that in these diagrams the points taken for the upstroke of *R* and the beginning of *P* were made to correspond exactly with those previously used by Lewis, thus maintaining in the present work the identical zero points of the former measurements. The variations from the normal electrocardiogram of the dog seen in some of the curves find an explanation in the fact that these are experimental electrocardiograms, taken after the thorax had been opened and the heart slung in the pericardium, thus unavoidably altering somewhat the normal relation of the heart to the plane of the standard lead.

The time at which the excitation wave arrives in the ventricle is ascertained by studying the ventricular surfaces separately. Activity is first in evidence in the central area of the right ventricle and appears a little later in the adjoining trabeculated area. The vortex of the left ventricle and the apex of the right are activated early. Excitation is next found simultaneously in the intermediate zones of both ventricles. The base of the right ventricle usually becomes active before that of the left, and the latest points to be reached are the conus of the right ventricle and the base of the left. The overlapping of readings and the variations in different animals are due to individual anatomical peculiarities, for it has been shown that for surface areas the spread of the excitation wave in the ventricle is governed by the distribution of the Purkinje system and the thickness of the overlying muscle. The surface reading for the central area coincides with the beginning of the upstroke of *R*, and that for the vortex of the left ventricle is 0.001 sec. later. The periods of activation of the trabeculated area, the right apex and the intermediate zones of both ventricles occupy positions on the upstroke of *R* in the order given. The reading for the base of the right ventricle bridges the summit. That of the conus is located on the summit or on the upper third of the down stroke. The period of excitation of the left ventricle is usually entirely on the down-stroke of *R* and extends about one third of the way to the base line. The relation of the surface activation of the ventricle and the electrocardiogram has been examined in seven dogs: Figs. 5, 6 and 7 are representative of the series. However, the earliest evidence of activity in the ventricle is not found in the surface readings but in those taken from the endocardium. The internal reading from the papillary muscle of the right ventricle occurs at the beginning of *Q* and the readings of the left septum and right and left apices occur before the beginning of *R*, while that for the base of the right ventricle is 0.001 sec. after it. The activation of the conus is later and covers a rather wide range, including about three-fourths of the upstroke of *R*, as shown in Fig. 8.

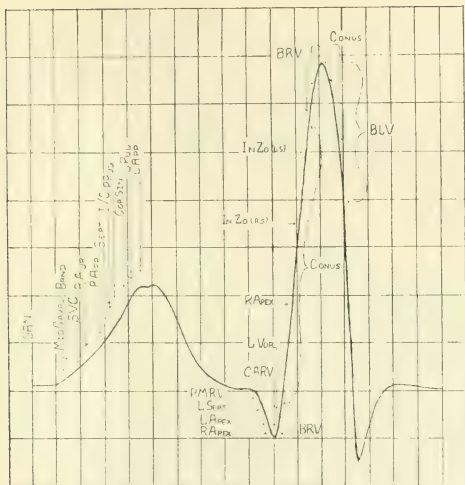


FIG. 8. A composite electrocardiogram with average figures for times of arrival of excitation wave. Abscissae, 0.01 sec.,

To summarise the foregoing details a composite electrocardiogram has been constructed, Fig. 8, and on it is indicated the general relation of the course of the excitation wave to the standard lead deflections. The data used are average figures from the experiments detailed in the original papers. The surface readings are written above and those from the internal contacts below the line. The average position of the sino-auricular activity for twenty experiments places it 0.01 sec. before the beginning of *P*. An area of muscle of 2 to 3 cm. diameter in the region of the sinus node is activated before *P* begins but without being registered in the electrocardiogram, presumably because the sensitivity of the string ordinarily used for standard leads (3 cm. 3 millivolts) is insufficient. The wave itself begins 0.003 sec. before the arrival of the excitation wave at the mid-caval region or the inter-auricular band. The activation of the left appendix occurs at the summit of *P*, and the intermediate points represent average positions (Table VII of the original paper!). The period of about 0.05 sec. from the time of arrival of the wave at the coronary sinus until it first appears in the

ventricle indicates approximately the delay in the auriculo-ventricular node. The relations of the points of ventricular excitation have been sufficiently described. It remains to recall that in each instance the reading is that of the *arrival* of the excitation at that particular point. The full development of the charge continues for about 0.01 sec., and to express the entire period of activation some such value must be added to the last reading. When this is done the remainder of *R* and *S* are accounted for and the agreement of the direct readings and the length of the *QRS* group of the axial electrocardiogram is such that the latter may be taken to indicate the duration of the spread of the excitatory process in the ventricle.

### *Summary.*

From the original experimental curves of Lewis and his co-workers on the spread of the excitatory process in the dog's heart certain standard lead *II* electrocardiograms have been taken and charted to scale, maintaining the original zero point, and against these curves the times at which the excitation wave arrives at the various places observed in the same dog's heart have been marked in chronological order. In the auricle the earliest point at which activity is observed is that of the sino-auricular node. The *P* wave begins 0.01 sec. later, at a time corresponding to the activity of the mid-caval region or the interauricular band. The reading for the left appendix, the latest point to become active, falls on the summit or the plateau of *P*, while intermediate points occupy slightly varying positions on the upstroke. The earliest activity in the ventricle, recorded internally at the papillary muscle of the right ventricle, coincides with the beginning of *Q*. For most of the surface points observed the time of arrival of the wave falls on the upstroke and near the peak of *R*, though occasionally late points of activation include the upper third of the downstroke. When a correction is made for its full development the period of spread of the excitatory process in the ventricle is found to be the duration of the *QRS* group.

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- <sup>2</sup> LEWIS (T.) and ROTHSCHILD (M. A.). "The excitatory process in the dog's heart." Part II. The ventricles. Phil. Trans. Roy. Soc., 1915, B, ccvi, 181-226.
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## SOME OBSERVATIONS UPON ATROPINE AND STROPHANTHIN.\*

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### PRELIMINARY OBSERVATIONS.

#### *A-V block in response to raised auricular rate.*

If the mammalian auricle is stimulated by means of rhythmic break shocks, and the rate of these shocks is gradually raised, eventually the auricle will fail to respond. It breaks into a condition of 2 : 1 or half-response. This half-response is due, as has been shown, to alternate stimuli falling during the refractory periods of previous responses. Foreshadowing this half-response as the rate is raised, is a state of depressed conduction in the auricular muscle which, as has been stated,<sup>11</sup> is also brought about by the relation of the stimuli to the end of the preceding refractory periods. The stimuli fall in the period which we term that of *partial refractoriness*. To produce steady 2 : 1 response in the unatropinised dog's auricle it is usually necessary to raise the rate of stimulation to 450 or 500 per minute.† The event which foreshadows 2 : 1 response, namely, lengthened transmission intervals from point to point of the auricular surface, occurs at lower rates: lengthening begins in the unatropinised auricle usually at a rate of about 350 per minute.

Phenomena which are parallel to these occur at the A-V junction. As the rate is raised there comes a time when the interval between the contractions of auricle and ventricle are lengthened; and, if the rate of stimulation is further raised, block occurs. As in the case of the auricular muscle, this block consists first of all of occasional dropped beats, progressing to a condition of temporary or persistent 2 : 1 response.

In the auricular muscle and in the junctional tissues there are therefore two comparable series of events, and each depends on the same cause, namely, a raised rate of response. Both being dependent on raised rate it

\* Carried out on behalf of the Medical Research Council. In all the experiments described in this paper the dogs were anaesthetised fully and throughout with morphia 9.03 gram., paraldehyde 10 c.c., and a sufficiency of ether.

† To produce it in the atropinised auricle, in which the refractory period is longer, requires somewhat lesser rates.

is difficult to avoid concluding that they are produced by similar mechanisms in the two situations. In the auricle they are now known to result from the relation of the stimuli to the preceding refractory periods: a similar conclusion seems inevitable in the case of the junctional tissues. That 2:1 response may result from alternate impulses falling during the periods of absolute refractoriness has been recognised<sup>15\*</sup>; but it has been shown only recently that widened transmission intervals may be produced by similar causes: this demonstration in the case of auricular muscle inevitably opens up the same question as regards the junctional tissues. Since widened intervals result from increased rate and lead up directly to dropped beats, and since the rates and associated disturbances of conduction form comparable series to those witnessed in the auricles of the same animals, then it seems justifiable to conclude that these widened intervals and dropped beats are not due to disturbance of a hypothetical and independent function "conductivity," but to the relation of the impulses to the preceding refractory period, as is proved to be the case in the auricular muscle itself.

The rates at which the widened intervals on the one hand and the dropped beats on the other occur may be taken as a gauge of the length of the refractory period of the tissue in which these phenomena are observed.

The following table (Table I) illustrates the rates at which conduction changes in the auricle and junctional tissues appear as rate of response is raised. The readings for the auricle are taken from a previously published paper<sup>12</sup> (Tables on page 249): the events at the A-V ring have been added after a further examination of the same plates. The A-V intervals expressed in the third column of the table have been measured from curves taken by contacts lying on the auricle: these curves yield sharp indications of the auricular beat (intrinsic deflections) and yield also indications of the ventricular beat: where these last are clear and sharp a reliable measurement is obtainable.<sup>†</sup> It will be seen from these tables that the A-V intervals begin to widen as rates of approximately 200-250 are reached. The auricular transmission interval usually begins to widen as rates of about 350 are reached. Failure of ventricular responses occurs at rates of about 300 to 350: failure of auricular responses is not shown in these particular tables, the rates of stimulation being insufficient to induce it, but it is known to appear usually at rates of 450 to 500 per minute.<sup>‡</sup> Thus, the rates necessary to produce comparable conduction disturbances range some 100-150 beats per minute higher in the case of the auricle than in the case of the junctional tissues: and we take this difference as an index of the

\* A form of clinical heart-block, supposed to arise in a somewhat similar manner, has been discussed by Hay and Wenckebach: it is characterised by dropped beats without a preliminary or accompanying lengthening of the A-V intervals.

† The interval given is not the P-R interval: with this it is not quite comparable: the readings are to be read relative to each other and are not to be taken as absolute values for comparison with P-R intervals.

‡ For illustrations see Table II.



TABLE I.

	Heart rates.	Auricular transmission intervals.	Auriculo-ventricular conduction. (A-V interval, etc.)
<i>Dog J R.</i>	233	0-0117*	0-13
	281	0-0107	0-14
	304	0-0104	0-17
	310	0-0106	0-16
	368	0-0108	2: 1, 1: 1 block
	375	0-0117	2: 1, 1: 1 block
	420	0-0101	2: 1, occasional 1: 1
	436	0-0126	2: 1, occasional 1: 1
	482	0-0139	2: 1 block
	517	0-0125	2: 1 block
<i>Dog J S.</i>	188	0-0149	0-14
	235	0-0142	0-14
	273	0-0141	0-15
	336	0-0148	Occasional dropped beats
	372	0-0158	2: 1, occasional 1: 1
<i>Dog J V.</i>	187	0-0140	0-17
	241	0-0137	0-17
	245	0-0144	0-21
	287	0-0150	Occasional dropped beats
	327	0-0154	2: 1, 1: 1 block
	361	0-0168	2: 1 block
<i>Dog J W.</i>	158	0-0180	0-16
	198	0-0173	0-16
	225	0-0180	0-17
	237	0-0157	0-17
	292	0-0153	Occasional dropped beat
	331	0-0167	2: 1, 1: 1 block
	372	0-0188	2: 1, occasional 1: 1
	388	0-0185	2: 1 block
	418	0-0194	2: 1 block
<i>Dog K D.</i>	243	0-0125	0-22
	290	0-0146	2: 1, 1: 1 block
	332	0-0191	2: 1 block
	362	0-0184	2: 1 block
	393	0-0195	2: 1, 3: 1 block
	420	0-0219	

\* Each of these values is an average of three measurements.

difference existing between the lengths of the refractory periods which are involved; it would appear that the refractory period of the junctional tissues is approximately 30 per cent. greater than that in the auricle itself.

We conclude that where A-V block occurs in response to raised auricular rate, that this block is due to the relation of the impulses to preceding refractory periods,\* and that it does not result from a deficiency in any independent function, "conductivity." When block occurs it occurs, for

\* Erlanger\* believes that impulses which impinge on the junctional tissues at raised rates are weaker, and consequently fail to excite the tissues. At present it is scarcely possible to decide if this factor also plays a part.

reasons presently to be stated, in the junctional tissues. This question may now be discussed.

It is to the *A-V* node that we naturally turn first in seeking the tissue in which block, resulting from raised rate, occurs; for this node is known to be a particularly susceptible structure.<sup>13</sup>

Definitely to exclude the ventricular muscle as the site of block we cite the following experiment.

The auricle is stimulated rhythmically at a rate to which it will respond, and at which the ventricle will not follow suit, the latter yielding a mixed 2:1 and 1:1 response. A record of this action is taken by means of lead *II* (top curve in Fig. 1). Simultaneous records are taken of the actual shocks (1, 2, 3, etc., in the central curve) and a direct curve from the auricular muscle, yielding an intrinsic deflection (1, 2, 3) at each response of the auricle (bottom curve). While the plate is running, the shocks are now transferred by means of a commutator to stimulating contacts on the ventricle. The commutator is switched over at such a rate that one shock fails to enter the heart: thus in the present figure shocks 1 to 8 entered the auricle, shock 9 falls during the movement of the commutator, and the remaining shocks 10 to 13, etc., fall upon the ventricle. The first shock to reach the ventricle yields a response, as do the succeeding shocks. Although the ventricle responds rhythmically and at the full rate, the auricle now fails to follow alternate impulses reaching it from the ventricle, the reversed block being somewhat higher in degree than the original forward block. Thus both auricle and ventricle are capable of responding at the rate of stimulation chosen, but the tissues uniting the two chambers are incapable of transmitting impulses at this rate, either in a forward or backward direction. The incapacity is clearly in the junctional tissues, and is not attributable to inexcitability of the ventricle in this case or of the auricle in the other. The experiment succeeds providing that the shocks are above the threshold value for auricle and ventricle, though they may be only just above these thresholds or well above them. It is to be observed that the last *R-R* interval of the figure (*R*<sup>4</sup> to *R*<sup>5</sup>) is one of the long intervals of the record; that being the case the refractory period of the last ventricular response to the auricle (*R*<sup>5</sup>) will be as long as any in the curve. The first ventricular shock enters the ventricle therefore at a disadvantage from our point of view. In many of our records the first direct response of the ventricle (to shock 10) falls after a longer interval. It seems to be a matter of indifference whether it falls early or late: if shock 10 yields a response, the successive responses are continued.

The experiment shows that when the ventricle fails to respond to the auricle because the latter is beating rapidly, it does so because it does not receive the impulse: it does not fail because the impulse falls within the refractory period of the ventricle itself.

## OBSERVATIONS UPON ATROPINE.

In a previous article<sup>11</sup> it has been shown (see Table XVIII of that article) that the highest rate at which the auricle is capable of responding to rhythmic stimulation is lower when the heart is atropinised. This effect is due to lengthening of the refractory period under atropine, so that alternate impulses fall more readily in the unresponsive phase of the auricular cycle. If an auricle is stimulated rhythmically at the highest speed to which it will yield regular responses, then an injection of atropine, in such a dose that the vagus is completely thrown out of action, is followed by irregular beating of the auricle or by 2 : 1 response : some stimuli now fall upon the refractory phase of the muscle and fail to yield responses. Table II sufficiently illustrates this phenomenon. Now 2 : 1 or half response is

TABLE II.

<i>Effect of carpal section and of atropine on response of auricle to rapid stimulation.</i>		
<i>Dog N J</i> (kilo 10.5)	Time.	Rhythmic stimulation of auricle, rate raised until auricular responses just missed; rate lowered a little to obtain regular responses; repeated and rate then maintained. The auricle gave regular responses at this rate, namely, 463 per minute for many minutes.
	11.9	Both vagi cut.
	11.10	Auricle missing one response in ten.
	11.10½	Auricle responding regularly.
	11.11	Auricle responding in short phases of alternate response (half rhythm).
	11.12	Atropine sulphate 0.0075 g. injected. Shortly afterwards strong right vagal stimulation was without influence on the heart.
	11.13	Pure half rhythm appeared almost immediately and continued.
	11.13½	Rate of stimulation lowered to ascertain lowest rate compatible with 2 : 1 response. The 2 : 1 response was maintained down to the rate 386 per minute.
<i>Dog N U</i> (kilo 8.3)		Rhythmic stimulation of auricle, rate raised until auricular responses missed occasionally; rate lowered a little to obtain regular responses; repeated several times to obtain constancy.
	11.54	The auricle gave regular responses at a rate of 480 per minute, with occasional short phases of 2 : 1 response. This rate maintained.
	11.54½	Atropine sulphate 0.0075 g. injected. Shortly afterwards strong right vagal stimulation was without influence on the heart.
	11.55	The auricle is now responding regularly to alternate stimuli.
	11.58	Same mechanism prevails.

foreshadowed by lengthened transmission intervals in the auricular muscle and these lengthened intervals occur at lower rates when the heart is atropinised than when it is not. It is true to say therefore that in certain circumstances atropine is capable of depressing conduction in the auricular walls. It predisposes the rapidly beating auricle to exhibit defects of conduction, it enhances the defect once this is present. The manner in which it does so is quite intelligible, even though this influence may seem paradoxical. Actually, as we have been able to show,<sup>11</sup> atropine has no effect upon the rate of fibre conduction in the auricle; its influence is upon the refractory period.

This effect of atropine is the converse of what we have previously described, namely, that if the rate of stimulation is driven sufficiently high to produce widened conduction intervals, or missed responses, stimulation of the vagus reduces the conduction intervals in the auricle to their original level or induces a 1:1 response.<sup>11</sup>

The demonstration of these effects of atropine upon conduction in the auricular wall are the more important because a parallel series of reactions may be elicited in the tissues which unite the auricle and ventricle. It is usual to think of atropine as a drug which, if it has any effect upon conduction from auricle to ventricle, will reduce the conduction intervals and remove, partially or completely, any tendency towards heart-block. That is but natural, in that heart-block between auricle and ventricle may be and often is the result of vagal inhibition, and atropine abolishes vagal tone.

But if the action of atropine upon A-V conduction is tested in circumstances comparable to those described for the auricular muscle, its effect is found to be different to its usual action. It has been our experience, in a long series of experiments, to note that the rate of rhythmic stimulation of the auricle necessary to elicit block between auricle and ventricle is lower in the atropinised than in the unatropinised heart; in other words, atropine predisposes to heart-block, when the main factor inducing such block is a high auricular rate. If the auricle is driven at so high a speed that the ventricle only just responds to it regularly, then an injection of atropine will usually render the ventricular responses irregular; a mechanism in which there is a regularly widened A-V interval (Fig. 2) gives place to one in which the intervals remain widened, or increase, and in which the ventricle from time to time fails to respond (Fig. 3). The reaction is similar to that produced in the auricular wall, and already described. It should be understood that both reactions are seen when full doses of atropine are given, doses sufficient completely to paralyse the vagus.\* The reactions are persistent effects. This point is emphasised because, as is now known, atropine in small doses will stimulate the vagus.<sup>6</sup> The reactions which we describe are not of this class; we are not describing temporary or initial effects but final ones. A frequent effect of atropine in full dose is first slightly to increase vagal tone and finally to decrease and abolish it; this leads, when the heart action is normal, first to slight slowing and finally to quickening of the beat. The paradoxical result which we describe in terms of block is a final increase of block as the result of atropine: actually an initial decrease of block has not been recorded, but the notes of our experiments speak of its happening on one occasion: the immediate sequel to the injection of atropine was a very temporary relief of pre-existing block, the final effect was a slight increase upon the original degree of block.

\* As proved in each instance to be the case, the dose used is  $\frac{1}{2}$  to 1 c.c. of a 1 per cent. solution of the sulphate.

TABLE III.

<i>Effect of vagal section and atropinisation on A-V conduction (the auricle beating rapidly).</i>		
<i>Dog N E</i> (kilo 10.5)	<i>Time</i>	Rhythmic stimulation of auricle; rate raised until ventricular responses are just missed; rate lowered a little to obtain regular response of ventricle; repeated and lower rate then maintained. The ventricle gave regular responses at this rate, namely, 300 per minute ( $P-R = 0.153$ of a second) for many minutes.
	11.35	Atropine sulphate 0.01 g.; shortly afterwards strong right vagal stimulation was without effect on the heart.
	11.36	Ventricle dropping occasional beats (recorded) and continued to do so for 11 minutes, when observation ended.
<i>Dog N F</i> (kilo 12.5)		Rhythmic stimulation of auricle; rate of stimulation raised until ventricular responses are just missed; rate lowered a little to obtain regular response of ventricle; repeated and lower rate then maintained. The ventricle gave regular responses at this rate, namely, 330 per minute ( $P-R = 0.180$ of a second) for many minutes.
	12.50	Atropine sulphate 0.01 g.; shortly afterwards strong right vagal stimulation was without effect on the heart.
	12.52	Ventricle dropping beats frequently (recorded) and continued to do so for 8 minutes, when the observation ended.
<i>Dog N G</i> (kilo 9.7)		Rhythmic stimulation of auricle; rate of stimulation raised until ventricular responses are just missed; rate lowered a little to obtain regular response of ventricle; repeated and lower rate then maintained. The ventricle gave regular responses at this rate of stimulation, namely, 330 per minute ( $P-R = 0.127$ of a second) for several minutes.
	11.36	Both vagi cut. Regular response of ventricle continued ( $P-R = 0.133$ of a second).
	11.38	Atropine sulphate 0.005 g. Shortly afterwards strong right vagal stimulation was without effect on the heart.
	11.40	Ventricle dropping occasional beats (recorded).
	11.45	Ventricle dropping occasional or frequent beats; observation ended.
<i>Dog N H</i> (kilo 17.3)		Rhythmic stimulation of auricle; rate of stimulation raised until ventricular responses are just missed; rate lowered a little to obtain regular response of ventricle; repeated and lower rate then maintained. The ventricle gave regular responses at this rate of stimulation, namely, 229 per minute ( $P-R$ interval = 0.172 of a second) for several minutes.
	11.23	Both vagi cut; one ventricular response in eight missed (records).
	11.24	Beats still dropped.
	11.25	Beats no longer dropped.
	11.26	Atropine 0.01 g. Shortly afterwards strong right vagal stimulation was without effect on the heart. The block did not increase, the $P-R$ interval falling to 0.113 of a second.
<i>Dog N I</i> (kilo 12.2)		Rhythmic stimulation of auricle; rate of stimulation raised until ventricular responses are just missed; rate lowered a little to obtain regular response of ventricle; repeated and lower rate then maintained. The ventricle gave regular responses at this rate of stimulation, namely, 351 per minute ( $P-R = 0.161$ of a second) for several minutes.
	11.6	Both vagi cut. Ventricle fails to respond one beat in eleven. This mechanism continued until 11.9
	11.9	Atropine 0.01 g. Shortly afterwards strong right vagal stimulation was without effect on the heart.
	11.10	Ventricle dropping one beat in four.
	11.15	Ventricle dropping one beat in two or three.

The explanation of these paradoxical effects of atropine is given by the similar reactions of the auricular muscle. The high rate of stimulation produces a critical relation between the length of the refractory period of the tissue involved and the inter-stimulus interval: atropine by prolonging the refractory period renders a lesser or greater number of the fibres incapable of responding to the on-coming stimuli. This change produces widened transmission intervals and, when all the fibres refuse to accept the stimulus, a dropped beat.

That the degree of *A-V* block produced by rapid stimulation of the auricle increases after atropinisation is a conclusion which we have come to from a number of scattered observations made during the progress of experiments undertaken from other points of view. The conclusion if warranted has seemed to us of so much theoretical interest that we have recently repeated the observations in a more deliberate manner. These recent results are given in the accompanying protocols (Table III).

These observations confirm our previous experience and add to it. The effect of atropine in increasing the preceding block is almost invariable. One exception (Dog *NH*) was noted; in this instance conduction improved after atropine. In this case the critical auricular rate necessary to produce block was inconstant and altered during the progress of the observation for unexplained reasons. These observations also show that section of both vagi will produce the same effect: though section is a less reliable method of bringing about the change. We have attempted to obtain the converse reaction, namely, a decrease in the grade of block by very weak stimulation of the vagi, but have not as yet succeeded. If an effect is seen, it is in the direction of increasing the block. It is presumed that the usual increase in *A-V* block under vagal stimulation is due to a depressant action of this nerve upon the rate at which excitability recovers, and that this action upon the nodal tissues more than counterbalances such reduction of the refractory period as vagus stimulation induces. This double action of the vagus, whereby on the one hand it tends to improve conduction and on the other to effect it adversely, is more fully discussed by one of us in a recent lecture.<sup>10</sup> The effect of vagal section or of atropinisation in increasing the *A-V* block which follows rapid auricular action, is one of the paradoxical reactions which confirms the view that these two opposed actions of the vagus exist.

#### OBSERVATIONS UPON A DIRECT ACTION OF STROPHANTHIN.

We shall now describe certain reactions of the dog's heart to strophanthin.\* which seem important theoretically and not without practical interest.

It is known that drugs of the digitalis series, including strophanthin, are

\* The strophanthin employed has been a crystallised preparation (from *g-strophanthus*) by Merck: it is the same preparation as used in the clinical service and is known to give decided effects in cases of auricular fibrillation in doses of from 1/250 to 1/100 of a grain.

In comparing the clinical and experimental actions of drugs it is of some consequence that these should be tested with a drug coming from a single source; preferable, as in this instance, from the same bottle.

capable of producing block at the A-V ring. The manner in which this block is produced in mammals has been the subject of much discussion. Cushny<sup>2</sup> injected strophanthin into large and medium sized dogs intravenously in doses of from 0.5 to 1.0 milligramme and more. Amongst other effects in the "first stage" of poisoning, he obtained vagal slowing, and sometimes profound slowing, of the whole heart: not infrequently he saw a curious condition in which conduction between auricle and ventricle seemed impaired. This last condition consisted in the appearance of a pause or pauses in the auricular or ventricular beating, and simultaneously the two chambers were discovered to be beating independently. Section of the vagi abolished these irregularities. Incomplete A-V block, the ventricle failing to respond to occasional or alternate auricular impulses, was not seen by Cushny; but it has been recorded by Tabora\* and, more recently, by Halsey. Halsey<sup>6</sup> usually gave strophanthin in doses of presumably 0.04 to 0.05 milligramme per kilo of body weight (*i.e.*, 0.4 to 0.5 mg. to 10 kilo animals) in morphinised or lightly etherised dogs, and recorded partial A-V block. Both these workers infer that the block is in part vagal.

In view of observations in which impaired A-V conduction appears to be of inhibitory origin, it has been natural to assume, as Cushny notes in a recent paper,<sup>3</sup> that the slowing of the ventricle in clinical fibrillation of the auricle, where this is produced by digitalis, is of a vagal origin. But Cushny holds a different view, believing the clinical effect to be direct upon the muscle. We do not propose to set forth the arguments for the one view or the other in the present article: the subject is fully discussed by Cushny in the paper last cited and is also reviewed along similar lines by one of us in a recent publication.<sup>9</sup> The question is not a simple one, but it seems to us that Cushny has shown that, in part at least, the clinical action may be a direct one upon the muscle: at the same time we do not think that it is yet established that the action may not also be in part inhibitory. The observations about to be recorded in part explain the nature of the direct action and help us to understand why members of the digitalis series exert an effect seemingly of an unusually profound kind upon A-V conduction when the auricles are fibrillating. Cushny believes that this profound reaction is due to an altered nutrition of the muscle in the case of fibrillation; of this we are not as yet convinced.

In attempts to compare the effects of the drug used clinically and experimentally, two factors seem to have received insufficient attention. The first is the rate at which the auricle is throwing off impulses to the ventricle: and the second is the dose of strophanthin given. In fibrillation of the auricles the impulses enter the A-V node at rates estimated in man at 400, and in dogs at about 500 to 600 per minute. Briefly, the rate at which the impulses are showered upon the node is such that a preliminary condition of block is always established; we have seen that the maximal rates of uniform ventricular response to the auricle driven by rhythmic

\* *Zeitschr. f. exper. Pathol. u. Therap.*, 1906, III., 499.



stimulation lie in the neighbourhood of 300 per minute in the unatropinised dog. The rate at which the impulses impinge is a factor which cannot be placed on one side in the discussion. Thus, it has been shown in the case of heart-block by compression and in asphyxial block that, with a given defect of conduction, the rate of the ventricle becomes slower as the rate of the auricle is raised: in other words, the degree of block (measured as the ratio of auricular to ventricular rates) is much enhanced by a rise of auricular rate.

The second factor is equally important: the dose of strophanthin usually given to dogs (in experiments) has been from 0.5 to 2 milligrammes: such doses are not used clinically, though the human body is many times heavier than those of the animals employed experimentally. The dose which has been used experimentally is often a lethal\* dose. Comparable doses in man are only reached in instances of accidental poisoning. The usual doses employed in clinical work are 1.250 repeated or 1.100 grain (approximately equal to 0.26 to 0.65 milligramme). Single doses equivalent to those customarily used in dogs† would amount to from 2.5 to 15.0 milligrammes, doses which are 10 or more times greater than those actually employed.

The purpose of the experimental observations is to ascertain how certain effects witnessed clinically are produced: a successful issue seems scarcely to be anticipated unless doses more comparable to those used clinically are employed in experiment. If these small doses are given to dogs in which the heart is beating normally, no very obvious effect is observed: presumably it is for this reason that the dose has been increased.

It is in the patient in whom the auricles are fibrillating that the clinical doses produce obvious reactions: and, so far as we are aware, equivalent doses have not been tried in the dog when a high rate of auricular beating is maintained.

As our experiments have shown us, if the auricular rate is maintained at a high point, effects are to be observed in the dog's heart when doses much smaller than those customarily employed in experiment are given. On occasion a distinct reaction is obtained with a dose of as little as 0.13 milligramme: a distinct reaction is always obtained with total doses of from 0.2 to 0.4 milligramme in dogs of about 10 kilos weight. The reactions seen in these circumstances are reactions preceding those of the first stage, as this is described in experiment, and they may be more comparable‡ to the therapeutic reactions.

\* The lethal dose of strophanthin is 0.124 mg. per kilo body weight in dogs (Jamieson<sup>2</sup>) and 0.1 mg. per kilo body weight in cats (Hatcher and Brody<sup>3</sup>; Eggleston,<sup>4</sup> Jamieson). The lethal dose in an average sized cat (2.5 kilo) is 0.25 mg.; the lethal dose in a medium sized dog (10 kilo) is 1.2 mg.

† Assuming man to be equally susceptible to the dog, and assuming a body weight of 50 to 75 kilos.

‡ Even so they are not entirely comparable: for our doses still exceed, when calculated per kilo body weight, those given to patients some three or four times. It may be that the human heart is somewhat more susceptible than the canine, though we think it probable that reaction in the dog would be seen with even smaller doses, providing that the auricular rate was raised to points above those which we have used. (NOTE: Subsequent experiment indicates that this is the case.)



## OBSERVATIONS.

The observations have been carried out on dogs weighing from 8.0 to 10.2 kilogrammes. The rate at which the excitation wave is carried from point to point in the auricle, and from auricle to ventricle, has been studied, the first by means of two pairs of direct contacts laid in line upon the auricular wall, the second by means of the usual lead *II* from the limbs. The indices of a reaction are three in number :

(1) Widening of the *P-R* interval, and subsequently dropped ventricular beats ;

(2) variations in the form and height of the intrinsic deflections from beat to beat in the curves taken direct from the auricle (these variations mark the first change in transmission through the auricular muscle itself) ; and

(3) widening of the transmission intervals from point to point of the auricular muscle.

Records were taken before and after the injections, and in each experiment at two or more rates of auricular beating. The auricle was driven at chosen rates by means of rhythmic break shocks.

The early effects of strophanthin have been best displayed in the *P-R* intervals (Table IV). They are clear in five out of six experiments : in the fifth experiment (Dog *MY*) the degree of block prevailing at the high rate of stimulation before the injection of strophanthin was undesirably high.\* The observations after strophanthin were made after a delay of 8-10 minutes following each intravenous injection, this period being allowed for the reaction to develop. Records at the high and low rate of stimulation, and with the normal rhythm, were taken in varying orders, but as quickly as possible in succession after each other. Where several complete observations follow a single injection, time intervals of about 5 minutes elapsed between the groups.

A distinct effect on *A-V* conduction was seen after total doses of 0.39, 0.26, 0.13 and 0.26 mg. in the first four experiments, and after 0.13 mg. in the last experiment. The reaction was displayed after these doses in the records taken while the auricle was beating at the highest rates (230 to 380 per minute). In two instances (Dogs *MR* and *NT*) the change was seen after the same dose in the records taken at both higher and lower artificial rates† : in the remaining experiments an additional injection was needed to produce conduction change at the lower rate of rhythmic response. With the possible exception of Dog *NT*, heart-block was not observed while the heart-beat was uncontrolled. The natural *P-R* interval was recorded in the last four experiments.

\* When a condition of 2 : 1, 1 : 1 response prevails as a result of raised rate, small increases in the degree of block, consequent upon the injection of strophanthin are not easily detected with certainty.

† In these experiments, the rates (230 and 280 ; 180 and 234) were either too close to each other to yield a decisive difference, or the dose was a little too large for its effect to be differentiated by rate.

TABLE IV.

*Effect of strephanthin on A-V conduction, etc.*

		LOW RATE.				HIGH RATE.				NORMAL RHYTHM.	
		Transmis- sion time.	P-R interval.	Complexes.	Rate.	Transmis- sion time.	P-R interval.	Complexes.	Rate.	P-R interval.	
<i>Dog M Q</i> (kilo 9.5) Strop. 0.13 mg.	165	0.0123	0.090	Regular	254	0.0120	0.128	Regular			
	170	0.0121	0.087	Regular	258	0.0111	0.125	Regular			
	175	0.0134	0.090	V. sl. variation	250	0.0110	0.129	Sl. variation			
	175	0.0123	0.091	V. sl. variation	258	0.0124	0.136	Sl. variation			
	175	0.0135 (0.0105) (0.0165) (0.0109) (0.0121)	0.101 0.104 0.104 0.104	Sl. variation Variation Variation	252 266 256	0.0113 (0.0132) (0.0184) (0.0169) (0.0168)	Frequent dropped beats Variation	Sl. variation Variation Variation			
<i>Dog M R</i> (kilo 10.1) Strop. 0.25 mg.	226	0.0119	0.129	Regular	287	0.0111	0.156	V. sl. variation			
	228	0.0114	0.125	Regular	280	0.0115	0.156	V. sl. variation			
Strop. 0.13 mg.	230	0.0109	0.141	Regular	280	0.0123	Frequent	Variation			
	235	0.0119	0.164	Regular	285	0.0120	dropped	Marked variation			
	230	0.0126	0.173	Sl. variation	280	0.0121	beats	Very irregular			

<i>Dog M S</i> (kilo 10.2) Strop. 0.13 mg.	230	0.0125	0.107	Regular	342	0.0110	0.137	V. sl. variation	180	0.077
	240	0.0128	0.105	Regular	340	0.0123	0.154	Sl. variation	172	0.078
	230	0.0132	0.107	V. sl. variation	345	0.0126	0.163	Sl. variation	172	0.082
	240	0.0135	0.114	Sl. variation	346	0.0135	Dropped heads		223	*
<i>Dog M T</i> (kilo 9.1) Strop. 0.13 mg.	268	0.0094	0.137	Regular	386	0.0087	Dropped heads	V. l. variation	187	0.089
	260	0.0075	0.138	Regular	377	0.0098	Dropped heads	Sl. variation	200	0.090
	260	0.0073	0.138	Regular	380	0.0103	More frequent dropped heads	Variation	200	*
	275	0.0099	0.105	Regular	402	0.0119	Dropped heads	Variation	209	0.083
<i>Dog M V</i> (kilo 9.2) Strop. 0.13 mg.	280	0.0101	0.105	Regular	396	0.0108	Dropped heads	Variation	187	0.083
	280	0.0100	0.108	Regular	392	0.0123	Dropped heads	Variation	195	0.084
	180	0.0130	0.144	Sl. variation	234	0.0144	0.120	Sl. variation	120	0.128
	185	0.0134	0.235	Regular	231	0.0120	2 : 1 block	Sl. variation	118	0.139
<i>Dog N T</i> (kilo 8.0) Strop. 0.13 mg.	185	—	0.193	Variation	229		2 : 1, 1 : 1 block	Variation	109	0.128

\* Not comparable.

Fig. 4 illustrates the curves from which the table is compiled. In Fig. 4a the auricle is being driven at a rate of 222 per minute and the *P-R* interval measures 0.107 of a second. Fig. 4c is a similar curve taken 8 minutes after the injection of the last of two doses of strophanthin (total 0.26 mg.). The *P-R* interval remains unchanged, measuring 0.107 of a second. Figs. 4b and 4d are the two companion curves, the auricle in each being driven at 343 per minute. In Fig. 4b the *P-R* interval is 0.137 of a second, a rise purely dependent on the rate of the auricular beating; in Fig. 4d it is 0.163 of a second, a further increase which is attributable to strophanthin (total dose, 0.26 mg.).

A further dose of 0.13 mg. was now given, and the effect is shown in Figs. 4e and 4f. At the high rate of stimulation (Fig. 4e) (346 per minute) dropped beats are frequent; at the lower rate of 219 per minute (Fig. 4f), a very slight increase of the *P-R* interval (as compared with Fig. 4a) is visible; the interval measures 0.114 of a second as compared to the old reading of 0.107 of a second. In the experiments there was no material change of the natural heart rate consequent upon the injections, thus, in two out of the four experiments in which the rates were recorded, these rose slightly after the injections; in two they fell slightly. While the heart beat naturally there was therefore little or no sign of inhibition of the auricle, such as has been described as occurring in the "1st stage" of poisoning. In three experiments when frequent dropped beats appeared after injections of strophanthin, while the auricle responded to the high rate of stimulation, we have fully atropinised the heart, and in another we have cut both vagi, without diminishing the grade of block. The block of our experiments is not of vagal origin; so far as it is ascribable to the drug, it is a direct action on the muscle.

A certain degree of heart-block was present at the high rate of auricular beating in each experiment before strophanthin was injected; the strophanthin in single or repeated doses increased the degree of this block. In this respect the conditions are similar to those met with clinically; for when the auricles are fibrillating many impulses fail to reach and stimulate the ventricle and strophanthin increases the number of impulses which fail in this manner. The nature and situation of the preliminary block, resulting from enhanced auricular rate, has been discussed, and it is concluded that it is due to the time relation of the descending stimuli to the refractory period of the muscle showing the defect; it has also been concluded that the block is situated in the *A-I'* node. The increase in the grade of this block by strophanthin is naturally ascribed to an increase in the length of the node's refractory period. This view also finds support from our observations upon the auricular muscle itself, presently to be described.

We conclude that an early action of strophanthin upon the tissues uniting auricle and ventricle in the dog is a direct action and consists in a lengthening of the refractory period in the fibres of the *A-I'* node. An action of this kind occurring in man would reduce the ventricular rate

of response to the fibrillating auricle, and would in part (we do not say wholly) account for the curious susceptibility of the fibrillating heart to strophanthin, as this is observed clinically. The view is consistent with the fact that, in patients who suffer from auricular fibrillation, the reduction of the ventricular rate by means of members of the digitalis series is the more certain, the higher the original rate of ventricular beating. Incidentally, the early and direct action upon the tissues uniting auricle and ventricle, observed in the dog, brings the observations upon the mammalian heart more closely into line with those which have been recorded upon the cold-blooded heart.

It is concluded that the direct action of the strophanthin is upon the A-V node for reasons similar to our conclusions that the block produced by simply raising the auricular rate is so situated. In several experiments while frequent dropped beats of the ventricle have been present in dogs under strophanthin, the auricle being driven rapidly, the rhythmic shocks have been rapidly transferred from auricle to ventricle. The result has been similar in every respect to that already illustrated (Fig. 1). Although, while the auricle is stimulated, the ventricle fails fully to respond, yet when the shocks are turned into the ventricle it responds to each shock successively; and it does so whether the shocks have a value but very slightly above the threshold point for the ventricle or are stronger. The failure of the ventricle to respond to each impulse from the auricle, while the latter is beating rapidly and the heart is poisoned with strophanthin, is not due therefore to lengthened refractory period of the ventricle, neither is it due to a "lowered excitability" of this muscle; the block lies in the junctional tissues. In the digitalised frog's heart, displaying A-V block, de Boer<sup>1</sup> definitely concludes that the block is in the muscle of the ventricle, the refractory period of which is increased; it may be that in this respect there is a contrast between the heart of the amphibian and mammal, though we do not regard de Boer's arguments as convincing.

#### *Action on the auricular muscle.*

The earliest sign of changed conduction in the auricular wall manifests itself as an irregularity in the amplitude of the intrinsic deflections of direct leads from the auricular muscle. Similar irregularities in the direct auricular curves are produced by increase of rate alone, providing the rate reached is sufficiently high; these have been described fully in previous communications, and have been ascribed to minor defects in transmission resulting from the wave encountering some refractory fibres in its path. The irregularities seen under strophanthin are the same, but are produced at lower rates of beating. If the auricular rate is raised to a point somewhat below that at which irregularity would be displayed and strophanthin is then administered, the irregularity appears. A dose of 0.13 mg. of the drug may suffice, though for such small doses the rate of beating has to be raised to a critical point. If records are taken while the auricle is driven alternately at a high rate and a

rate some 100 beats per minute lower, the irregularity tends first to appear or first to increase in its degree at the high rate\* as a result of small repeated doses of strophanthin.

The meaning of these reactions is not in doubt. Irregularity of the record is produced when the stimuli fall sufficiently close to the end of the preceding refractory periods: the gap between the two is lessened as the heart rate is raised because the stimulus falls earlier; it is lessened by strophanthin because this drug lengthens the refractory period.

An action of drugs of the digitalis series upon the length of systole, is one which has been known for many years and upon which all observers are agreed: it is conspicuous. It is usually and rightly assumed that the length of the refractory period widens correspondingly. Straub<sup>11</sup> found the refractory period lengthened by antiarin. Cushny<sup>2</sup> noticed great lengthening of systole in the first stage of poisoning in the dog, but attributed it to the accompanying retardation of rate, a factor which has necessarily to be taken into account. We know of no actual measurements of the refractory period in the mammalian auricle under strophanthin or of any observations on the allied drugs while the rate is maintained; and have considered it advisable to make direct observations. The method used has been described fully in a previous article<sup>11</sup> (page 85). The atropinised heart is driven by means of rhythmic break shocks applied to the auricle; the testing shocks have consisted of occasional break shocks many times the threshold value and applied at the same point. In the last two experiments the threshold value of the testing shocks has been recorded in our notes; and in each of these experiments also the refractory period under a given dose of strophanthin has been tested with the coil at different points, each of which should, in our opinion, give the measure of the absolute refractory period. On neither occasion was there a fall in the measurement when the stronger stimuli were used. The values may be taken therefore to represent the absolute period and not to include any portion of the relative period. Our table shows that the refractory period widens from the values 0.092, 0.118, 0.104 and 0.121 of a second to 0.161, 0.158, 0.135 and 0.156 of a second with doses of 0.13 mg.: a second and equal dose forces it to 0.188, 0.175, 0.160 and 0.200 of a second. The lengthening is conspicuous,<sup>†</sup> being from 50 to 100 per cent., with total doses of 0.26 mg.

When the amplitudes of the deflections begin to vary in direct auricular leads under the influence of strophanthin, a further small dose (0.13 mg.) will

\* Sometimes it appears or increases simultaneously at high and low rates. This is a question of the rates used and the dose of the drug given.

<sup>†</sup>Tait<sup>1</sup> concludes that the absolute refractory period of the heart is not prolonged by Yohimbine; but the previous text and his figures scarcely warrant this statement. They warrant, perhaps, the statement that Yohimbine does not prolong the refractory period beyond the summit of systole. It is not possible to measure the length of systole in Tait's curves; there is the further difficulty that very different rates of beating are compared.

It is to be emphasised that our measurements apply to the *atropinised* auricle: the refractory period cannot be measured so satisfactorily in the unatropinised organ, though in one unatropinised auricle we have recorded an appreciable rise after strophanthin (0.13 mg.).

TABLE V.

*Refractory period before and after strophanthin. (Atropinised auricle.)*

Dog .. ..	M Y (10.1 kilo).				M Z (9.5 kilo).		
	Before.	After (total in milligr.).			Before.	After (total in milligr.).	
		0.13	0.26	0.33		0.13	0.22
Auricular rate	200	210	210	212	209	212	224
	0.183				0.173		
	0.151				0.140		
	0.147				0.139	0.246	
	0.143				0.137	0.220	
	0.125	0.185	0.236		0.134	0.218	0.217
	0.124	0.179	0.227		0.133	0.214	0.216
	0.112*	0.173	0.219	0.217	0.125	0.191	0.191
	0.103	0.169	0.203	0.206	0.123	0.187	0.186
R.P.	0.098	0.168	0.197	0.181	0.122	0.158	0.186
	0.087	0.154	0.180	0.176	0.115	0.158	0.165
	0.086	0.145	0.172	0.152	0.113	0.150	0.155
	0.084	0.134	0.170		0.111	0.130	0.142
	0.074	0.131	0.154		0.104	0.129	0.141
	0.073	0.128			0.098		
	0.071	0.120			0.085		
		0.120			0.074		
		0.111			0.059		
		0.106					
		0.106					
		0.085					
Threshold coil at	—	—	—	—	—	—	—
Coil at .. ..	8 cm.‡	8 cm.	8 cm.	8 cm.	8 cm.	8 cm.	6 cm.

\* The readings in heavy type indicate "no response."

† The secondary coil begins to overlap the primary at 9 cm.; the initial threshold for dogs usually stands at about 13 cm..

Dog .. ..	N S (10 kilo).				N T (8 kilo).			
	Before.	After (total in milligr.).			Before.	After (total in milligr.).		
		0.13	0.13	0.26		0.13	0.13	0.26
Auricular rate ..	182	187	190	188	180	183	183	183
		0.179		0.218				
		0.161		0.209				
		0.160	0.194	0.206				
	0.130	0.160	0.178	0.205	0.157	0.248		0.239
	0.127	0.158	0.178	0.205	0.154	0.235		0.225
	0.119	0.152	0.166	0.198	0.143	0.210	0.221	0.222
	0.114	0.145	0.164	0.179	0.136	0.171	0.186	0.215
	0.113	0.145	0.159	0.177	0.136	0.167	0.166	0.203
	0.110	0.141	0.157	0.169	0.135	0.158	0.164	0.200
R.P.	0.104	0.140	0.166	0.166				
	0.104	0.130	0.143	0.155	0.107	0.154	0.163	0.200
	0.099	0.116	0.140	0.137	0.101	0.143	0.157	0.193
	0.091	0.114	0.137	0.137	0.096	0.141	0.153	0.186
	0.089	0.105	0.137	0.136	0.092	0.139	0.152	0.185
	0.080	0.094	0.133	0.130	0.086	0.137	0.150	0.175
	0.067		0.115	0.126	0.075	0.132	0.124	0.174
			0.091	0.115				0.171
				0.113				
				0.108				
				0.103				
Threshold coil at ..	16.5 cm.	—	12.5 cm.	10.5 cm.	13.25 cm.	13.75 cm.	—	12.5 cm.
Coil at .. ..	5 cm.	5 cm.	2 cm.	2 cm.	6 cm.	6 cm.	2 cm.	2 cm.



widen the transmission intervals from point to point of the auricular wall. This accords with our experience of the auricle responding to rising rates of rhythmic stimulation only: the sole difference being that under strophanthin the rate of response which widens these intervals is lower. The widened transmission interval and the deflections of varying height are both attributed to fibre blocks. These changes are progressive under strophanthin as the doses are repeated, until eventually curves of a very disorderly type are recorded. A simple form of irregularity is seen in Fig. 5. The auricle is responding to interrupted break shocks applied to the right appendix, at a rate of 392 per minute, strophanthin amounting to 0.19 mg. had previously been injected. In lead *II* partial *A-V* block is observed, the ventricle failing to respond at each fourth cycle approximately. Two simultaneous and direct records from the line of the right appendix are also shown: the second (*P*), taken from points nearest to the stimulating electrodes, shows definite variations in the amplitude of its deflections. A further dose of 0.07 mg. strophanthin (total 0.26 mg.) was now given to this animal, the rate of stimulation being maintained. Shortly, the degree of *A-V* block increased and the irregularity shown by the direct curves became much more pronounced. It became especially pronounced in the distal lead from the appendix (Fig. 6); in this the curve is of a peculiar form. It should be compared with Fig. 6 of a previous article<sup>12</sup>, and with the curves illustrating "twin deflections," as these are seen in the direct curves of the fibrillating auricle (*Heart*, Vol. VIII, page 206): it is a form of curve with which we are now very familiar, and its origin has been discussed fully. Evidence has been advanced to show that it is due to local block in the auricular wall, the muscle being in a state of partial refractoriness as the wave passes through it. The irregularity of this and similar records suggests that strophanthin not only prolongs the refractory period but that it may influence the state of partial refractoriness which the muscle presents when it beats rapidly; for the degree of disorder shown is greater than with a rise of rate alone. A somewhat similar idea has occurred to Tait<sup>15</sup> in his work on Yohimbine.

That the irregularities in the auricular records described result from the time relations of the stimuli to the refractory state (absolute or partial) of preceding contractions, is scarcely to be doubted from the close resemblance which they bear to those described in previous articles: but to set the matter at rest we have again employed vagal stimulation as a test. If these irregularities are the result of change in the rate of fibre conduction, they should not be influenced by vagal stimulation, for the latter, as we have shown, does not affect the rate of conduction through individual fibres. On the other hand, if they are dependent upon the length and constitution of the refractory period, we should expect them to be abolished by vagal stimulation. Such has proved to be the case, as the companion curves (Figs. 7 and 8) sufficiently illustrate. In the last the curves of the direct leads are regular or the irregularity has very greatly diminished. The irregularities discussed are not sensibly altered either by vagal section or by



full atropinisation; in so far as these procedures influence the curves at all, they influence the irregularity adversely. It is to be stated that, as was the case in the present instances, the irregularities described are produced before the electrocardiogram of the naturally beating heart is appreciably modified.

If, however, the heart is poisoned a little deeper, changes of a profounder kind, though related to those described, set in. The auricle fails to respond to stimulation, at first occasionally at high rates of stimulation, then occasionally or frequently at lower rates of stimulation, until finally it becomes altogether irresponsive. Between the first and last stage (that which precedes death of the muscle) are many intermediate stages; in this phase a number of very curious curves are to be obtained. They vary greatly from experiment to experiment and vary much in the order in which they appear: we propose to describe a few which are relevant to the foregoing observations.

Our view of the irregular curves illustrated in Figs. 5 and 6 is that they represent stages of a developing intra-auricular block. The records now to be described demonstrate this block unequivocally; these were taken from somewhat later stages of poisoning. Thus Fig. 9 is from the same animal as Fig. 6: it was taken 40 minutes after the latter, and 20 minutes after the last dose of 0.07 mg. of strophanthin (total 0.33 mg.). Three curves are shown: the upper from the limb lead (lead *II*) and the middle and lowest curves being taken by direct leads from the inferior caval region of the auricular wall and right appendix, respectively. At this stage of the experiment the strength of the rhythmic shocks entering the tip of the appendix had been much increased\* and the shocks themselves appear as steep deflections (*s, s*) in the lowest curve. For the first few cycles of the record these shocks alone appear in the appendix curve; in the caval curve there are three small elevations, *v*, which clearly correspond to movements of the ventricle. Briefly, neither the record from the inferior caval regions nor from the appendix shows sign of muscular activity; these portions of the auricle gave no visible contractions, and the strings recorded no electrical discharge. The auricle seemed at a standstill and quite inexcitable. The inspection of the chamber and the two direct curves are sufficient evidence of standstill in the exposed part of the right auricle: but not for the whole auricle, for the record from lead *II* demonstrates that some deeper portions were still active though beating slowly. Three distinct waves, *P*, appear in the early part of this record. It appears from this record, therefore, that a section of the auricle had been thrown out of action. This state was but temporary, it occurred phasically: the beginning of an irregularly active phase is shown in the last half of the same figure. Here are a number of variable deflections, *a, b, c*, etc., in the middle record, which speak for activity of the muscle beneath the corresponding contacts: simultaneously a minute deflection, which grows in amplitude and steepness as the record

\*To compensate for the fall of auricular excitability.

proceeds, appears in the lowest curve. These deflections of the last part of the curve coincided with the appearance of visible contractions of the muscle and with a notable growth in the size of the waves *P* in lead *II*. Physically, therefore, the wall of the right auricle passed in and out of action. When it passed into action it appeared to respond to the stimuli. We say so because it beat at a high rate, rather than because a complete relation can be established between shocks and responses, and because, when the rhythmic shocks were withdrawn, a normal heart action was resumed at once. It is notable, however, that the response is first most complete in the caval region and not in the appendix itself, where the shocks enter. From this it is judged that the excitation waves passed at first through a very limited path and failed greatly to impress their passage upon the appendicular contacts.

A second record (Fig. 10), taken from a different animal, and after heavier poisoning, illustrates a similar condition. The total quantity of strophanthin given was 1.3 mg. (a lethal dose), and the record was taken about 30 minutes after the second of two equal injections. The tip of the auricular appendix was stimulated rhythmically at a rate of 183 per minute. The appendix (upper curve) responds to the stimuli after intervals which change throughout the record: sometimes there is no response. The action of the muscle of the superior cava was phasic; sometimes it contracted quickly and rhythmically, then abruptly the picture would change and no contraction would be visible. The record (lower curve) shows only the shocks of stimulation for five cycles, and these are followed by responses (*e. f. g.*, etc.) at intervals which, while they are not quite regular, are almost so. In the beginning of the record, a large area of muscle clothing the superior cava is out of action, at the end the cava is beating somewhat more rapidly than the appendix. A diagram is intercalated, which attempts to relate the stimuli (*s. s.*, visible in both records from place to place) with the responses of appendix and cava, respectively. This relation cannot be expressed in detail with certitude: but a relation must be assumed which shows the appendix now responding without the cava, and now the cava without the appendix. The auricular beats of this record were not spontaneous: their dependence upon the rhythmic shocks was easily shown by discontinuing the latter, when the normal rhythm was at once resumed.

Similar records to these are sometimes obtained in the later stages of poisoning when the auricle is uncontrolled by rhythmic shocks, and these have also been described by Tait in Yohimbine poisoning.<sup>15</sup> Fig. 11 is a record from a dog taken 60 minutes after the last of three doses of strophanthin (total dose 0.39 mg.) and after section of both vagi. When this plate was taken there were no visible contractions of the exposed right auricle, and the only deflections in the direct leads (*P* and *D* from the base and apex, respectively, of the right appendix) are of ventricular origin. Nevertheless, portions of the auricle were active, as the *P* waves of lead *II* demonstrate. This condition of the auricle gave place at short periods to a rapid and

regular action of the auricle, each beat of which gave a ventricular response. The record, Fig. 12, is to be compared with the last figure. The muscle of the base of the appendix is now active and recording the prominent deflections *a, a, a*. Response of the tip of the appendix is uncertain, the deflections being less well defined. Curves of these types were alternately recorded many times, as the exposed part of the auricle passed into a state of quiescence or became active.

Periodic standstill of the visible auricle, while the ventricle continues to beat, was described by Cushny.<sup>2</sup> Such standstill of the auricle may be more apparent than real in poisoning by strophanthin. A large portion of the auricular tissue may become inactive while another hidden portion retains its activity: as to whether this limited active portion ever controls the movements of the ventricle, giving rise to an apparent though not truly independent rhythm, we are unable to decide.

*Strophanthin and its direct effect on conduction.*

In studying the effects upon A-V conduction of strophanthin, in the doses in which we employ the drug, we have seen that conduction is manifestly altered only when the rate of auricular beating is high. An abrupt change in conduction, a change in the direction of depression, which comes when the auricular rate is gradually raised, is characteristic of that form of defective conduction which develops when the stimuli fall close to the end of the refractory periods. A similar change in A-V conduction occurs in response to change of rate alone: in strophanthin poisoning the level at which depressed conduction is witnessed is lowered and we suppose it to be lowered because strophanthin prolongs the refractory period of the node.

Similar arguments apply to the muscle of the auricular wall. Repeated doses of strophanthin fail to alter the rate at which impulses are transmitted through the tissue, providing that the rate at which the auricles beat is natural: but if the auricular rate is raised, then widened intervals are demonstrated and in general these are shown earlier in the poisoning if the rate at which the auricle is driven is higher.\*

We conclude that strophanthin, in the doses in which we employ it, has no effect on the rate at which individual fibres conduct their impulses, but that all the phenomena of depressed conduction witnessed by us in these experiments may be ascribed to a change in the refractory period of the muscle, whereby at rates of stimulation sufficiently advanced, the impulses travel through muscle in a partially refractory state.

\* Under strophanthin and when the auricle is driven rapidly the form of the deflections from direct auricular leads usually changes: this change not infrequently introduces errors of measurement sufficient to destroy the value of the readings.

*Summary of conclusions.*

1. If the auricle is stimulated rhythmically by means of break shocks, and the rate of stimulation is raised, a widening of intra-auricular conduction intervals is observed: a little later the auricular muscle fails to respond to each shock. Similarly, when the auricle is driven at increasing rates, the *A*-*V* interval widens and shortly afterwards ventricular beats are missed. Both series of phenomena are attributed to the relation between the inter-impulse intervals and the length of the refractory periods of the muscle concerned.

2. The range of rates at which comparable events occur is considerably lower in the case of the *A*-*V* junction than in the case of auricular muscle.

3. The refractory period of the junctional tissues is about 30 per cent. longer than is that of the auricular muscle.

4. When *A*-*V* block occurs between auricle and ventricle in response to raised auricular rate, the site of the block is the *A*-*V* node, and the block occurs in this situation because the refractory period of the *A*-*V* node is relatively long.

5. Atropine by depriving the heart of its vagal tone increases the length of the refractory period, and consequently disturbed intra-auricular conduction and disturbed conduction at the *A*-*V* junction, resulting from increased rate of beating, are increased by atropine.

6. Strophanthin can be demonstrated to affect the muscle of the dog's heart in doses smaller than those usually employed, if a high rate of auricular beating is maintained.

7. The earliest action seen in our experiments has been a direct one on the muscle and consists essentially in a widening of the refractory period.

8. This widening of the refractory period decreases the gap between its termination and the succeeding impulse, and, as a consequence, those disturbances of conduction which are seen under simple acceleration of the auricle are manifested at lower rates when the muscle is poisoned.

9. Strophanthin in the doses employed does not alter the rate at which the fibres conduct their impulses; the conduction disturbances which are witnessed are of a distinctive kind and depend upon the relation of the impulse to the foregoing refractory period. The disturbances are dependent therefore not only upon strophanthin poisoning but upon the rate at which the muscle is responding.

10. It seems probable that when strophanthin and other members of the digitalis series block (by direct action on the muscle) the impulses of a fluttering or fibrillating auricle from passing to the ventricle, they do so, in part at least, by prolonging the refractory period of the auriculo-ventricular node.

11. In the later stages of strophanthin poisoning in dogs a condition of intra-auricular block is developed. This is also a refractory period effect; the refractory period appearing to vary in different parts of the muscle, rendering some parts irresponsive while other parts are capable of response to impulses which reach them.

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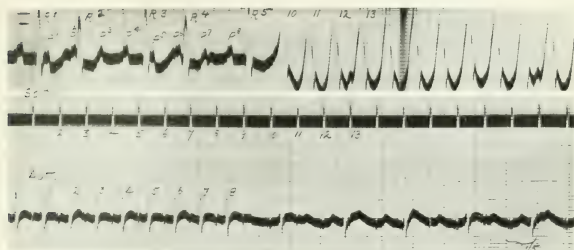


FIG. 1. *Don. M. B. Record No. 1.* Simultaneous curves from lead II, from the primary coil of the stimulating induction coil, and from a direct auricular lead. Shocks 1 to 8 fall upon the right ventricle respectively; the auricle responds regularly, the ventricle responds in a normal 2:1, 1:1. Shock 9 does not reach the heart, it falls during the movement of the contraction. Shocks 10 to 13, etc., fall upon the base of the right ventricle and yield irregular ventricular responses; the auricle responds at the half rate. The standard for lead II is 1 centimetre = 1 millivolt; for the direct lead approximately 1 millimetre = 1 millivolt. The standards apply to the remaining figures. Time in this and subsequent figures is the real length of a second, unless otherwise stated.



FIGS. 2 and 3. *Don. M. B. Records 1 and 5.* These two records are similar. In each is a simultaneous curve from lead II, from the stimulating coil and from the auricle direct. In Fig. 2 the auricle is being driven at a rate of 343 per minute; the ventricle is just capable of responding to each auricular impulse. In this curve the A-V interval is a little longer than the interval between two ventricular beats. Fig. 3 is a similar record taken a few minutes later, while the heart was fully under atropine. Occasional responses of the





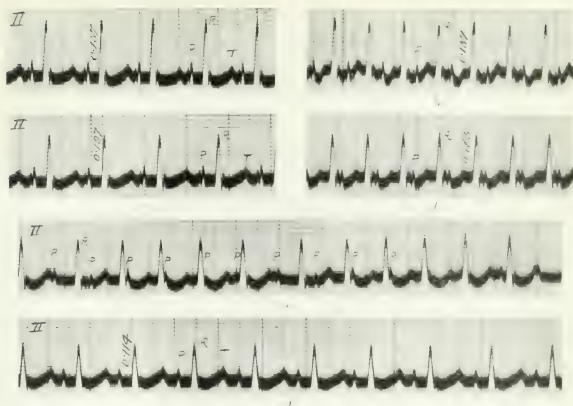


FIG. 4 (cont.). Dog M S. (Records 4, 5, 11, 10, 13 and 15, respectively.) S.N. curves from lead II showing the effects of increased auricular rate and strophanthin upon A.V. conduction.

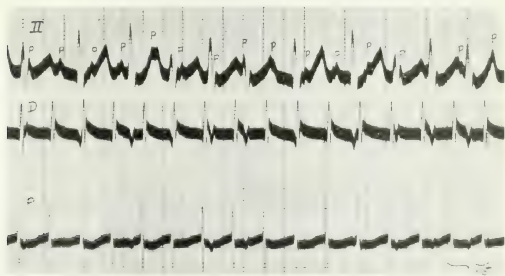


FIG. 5. Dog M V. (Record 17.) Simultaneous curve from lead II and from two chest leads from the auricle. P—curve from lead proximal to and D—curve from lead distal to point rhythmically stimulated. The shocks entered the auricular appendix and the two contacts were in line with this.

The auricle is being stimulated at a rate of 392 per minute and responds to each shock, but the deflections are irregular in the proximal curve. The ventricle fails to respond occasionally.



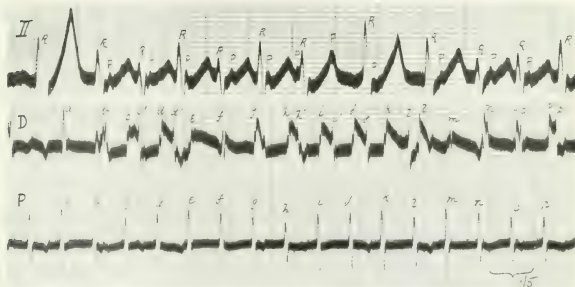


Fig. 6. *Lead II, Record 2.* The same, 8 minutes after the injection of the second dose of 0.06 mg. of strophanthin (total 0.2 mg.). The degree of A-V block has increased and the distal curve from the auricle has now become grossly irregular.

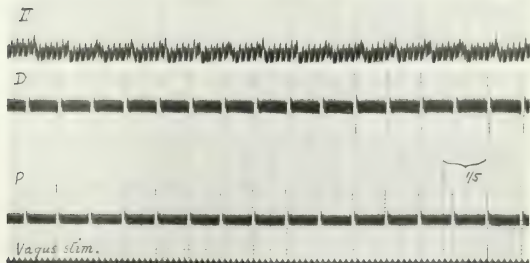


Fig. 7. *Lead II, Record 18.* A comparison record to that of Fig. 6, and taken immediately after it, with the heart under the influence of right vagal stimulation. The ventricle is at a standstill and the original irregularity of the deflections of the proximal lead has disappeared.



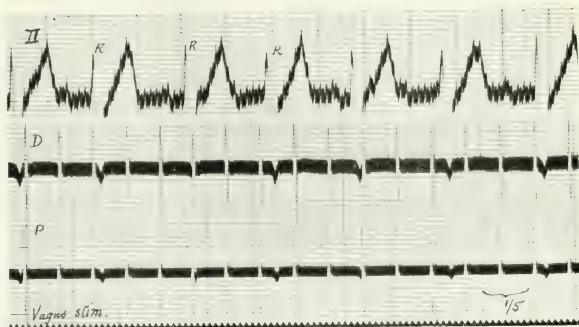


FIG. 8. *Dog M F. Record 21.*—A companion record to that of FIG. 6. The heart is now under right vagal stimulation. The rate of the ventricular action is lowered; the ventricle now seems to be beating independently. The gross irregularity originally present in the distal curve, and the lesser grade in the proximal, are almost abolished.

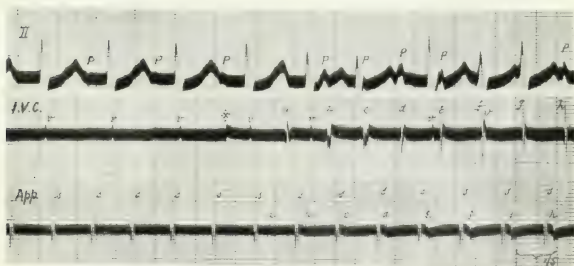


FIG. 9. *Dog M F. Record 18.*—Simultaneous curve from lead II, and direct leads from the inferior vena caval (I.V.C.) and right appendicular (App.) regions of the auricle. At a later stage of poisoning, and showing temporary and partial standstill of the auricle.



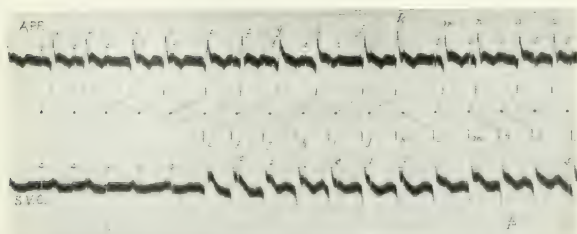


Fig. 10. *Dog M.S. (Record 30)*. Spontaneous activity by direct leads from the right auricular appendage and from the superior vena cava, strong in a normally intact block of atrioventricular block, long interval during presentation of atropine 0.01. The strophanthin is being administered intravenously at a rate of 184  $\mu$ g./minute.

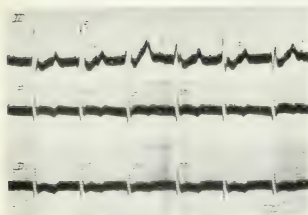


Fig. 11

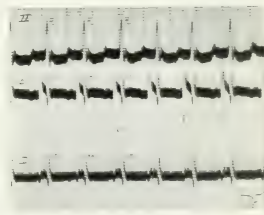


Fig. 12

Fig. 11. *Dog M.S. (Record 32)*. Spontaneous curves from lead II and from two pairs of contacts placed on the right auricular appendage; the heart beats were spontaneous and are taken from an animal in a relatively late stage of strophanthin poisoning and after section of the vagi. In lead II *P* (auricular) beats are most conspicuous; *P* (ventr.) is barely shown. In the curves taken from the superior vena cava there are no auricular deflections, but ventricular deflections only (compare with next figure).

Fig. 12. *Dog M.S. (Record 31)*. A similar record from the same animal and taken immediately before that of Fig. 11. The ventricular deflections (*r*) of the direct leads are here seen to be preceded by auricular deflections (*a*).





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OBSERVATIONS RELATING TO THE ACTION OF QUINIDINE  
UPON THE DOG'S HEART; WITH SPECIAL REFERENCE  
TO ITS ACTION ON CLINICAL FIBRILLATION OF  
THE AURICLES.\*

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THE following experiments were undertaken for the purpose of explaining the action of quinidine† upon the mammalian heart, and especially upon the mammalian auricle, with a view to ascertaining the action of this drug in cases of clinical fibrillation.

Dogs of approximately 10 kilos body weight have been fully anaesthetised with morphia (0.03 gram.), paraldehyde (10 c.c.) and ether and prepared for observation. The right auricle is exposed, the heart being slung in the pericardium. Electrodes are fastened to the right fore-limb and left hind-limb (lead *II*); four non-polarisable contacts are placed on the body of the auricle and in line with the appendix and these form a proximal and distal pair of electrodes, each pair being connected at will to the string galvanometer. Into the tip of the auricular appendix a pair of fishhook electrodes is fixed, through which break shocks may be sent singly or rhythmically into the auricle. The records taken are of several kinds. (a) Thus curves from lead *II*, showing the mechanism of the heart as a whole, are taken in combination with a curve from one pair of the contacts on the auricle. The combination is used in studying the auricular and ventricular rates and the *P-R* intervals. Where heart-block appears, the simultaneous direct auricular lead is of value in precisely timing the auricular systole, where its beginning is obscured in lead *II*. The combination is

\* Undertaken on behalf of the Medical Research Council. A preliminary account of these observations has appeared in the *British Medical Journal*, 1921, II, 515.

† Quinidine sulphate has been employed, being dissolved in normal saline and injected into the femoral vein. The quinidine sulphate employed contains 17 per cent. of hydroquinidine sulphate, but is otherwise pure. The same preparation has been used in the clinical services, and was the preparation used by Drury and Hiescu in the observations of their recent report (*Brit. Med. Journal*, 1921, II, 511). The comparison of clinical and experimental effects is consequently unaffected by the impurity of this commercial preparation. The action of the two alkaloids is similar (more recent observations).

used for the spontaneous heart beat and for responses to a fixed rate of rhythmic stimulation: these stimuli, consisting of isolated break shocks, are thrown into the auricular appendix at a rate of about 200 per minute. (b) If the two pairs of contacts on the auricle are connected to two recording fibres, and the appendix is stimulated rhythmically, then the records obtained may be measured to show the interval elapsing between the arrival of the excitation wave at proximal and distal pairs (the distance separating these being uniformly 8 millimetres) and this interval (inter-intrinsic interval of Table I) is an index of conduction in the auricular muscle. (c) A single direct curve is inscribed simultaneously with a record of rhythmic break and occasional make and break shocks, the recording current being derived directly from the primary circuits of the inductoria, in the manner fully described in an earlier paper.<sup>8</sup> This combination is used in estimating the absolute refractory period of the muscle.

A complete series of records is taken before quinidine is given and is repeated one or more times after each injection of the drug. We have examined a series of atropinised and a series of unatropinised animals: in the latter the refractory periods have not been observed, being in these circumstances unreliable.

The observations under quinidine have been begun about 5 to 6 minutes after each injection; the idea being to allow the full action to be displayed. A series of observations, omitting only the refractory period, occupies usually 2 minutes: if the refractory period is also estimated an extra 5 to 10 minutes must be allowed.

As the full action of a dose is not at once reached, and as recovery is usually not long delayed, the times of the separate observations are of consequence. These are stated in a column of our tables (Table I and II) as are also the numbers of the plates. These tables are in reality tabulated protocols of our experiments; as protocols, Table I and II are however incomplete: other observations were undertaken and will be found in the remaining tables of this article. From the tables as a whole the complete protocols may be reconstructed if this is desired.

Four experiments are illustrated in Table I: these dogs were unatropinised. In the case of *Dog N.M.*, as a preliminary, three plates were taken (Records 1, 2 and 3), and from these the natural rate of the heart beat and its associated *P-R* interval, the rate of rhythmic stimulation (*i.e.* 195) and its associated *P-R* interval, and auricular conduction (inter-intrinsic interval) are measured, as is also the length of the *Q.R.S.* group of deflections. The threshold for rhythmic break shocks at the same rate of stimulation is stated in the last column. These observations occupied altogether 6 minutes (11' 10" to 11' 16").\* At 11' 24" 0.1 gramme of quinidine was injected, and the series of observations detailed above was repeated

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\* Observations upon the vagus (Records 4 to 7) are omitted at this point in the table (see Table V, *Dog N.M.*).

at 11·28' to 30', at 11·46' to 48', etc. This description sufficiently illustrates the arrangement of our tables. Table II. comprises observations on four atropinised dogs and is similarly arranged, except that the refractory period of the auricle has been added. The effects of the quinidine injections\* may be separately considered.

*Effect on sino-auricular rhythm.* The effect is practically constant. The rate is retarded. Starting as high as 135 to 190 beats per minute it is usually lowered considerably by the first injection: while the retardation may occasionally be slight it more usually amounts to 30, 40, or 80 beats per minute. If a sufficient time elapses before a second injection, there may be some recovery of rate: this recovery begins normally about a half-hour after the injection. A second dose produces a further lowering, and after repeated doses such rates as 60 to 80 beats per minute are often seen. These effects are in general similar in the atropinised and unatropinised heart, and are ascribed therefore to a direct action on the muscle. Our observations are confirmatory of those obtained by Schott<sup>12</sup> upon guinea pigs† and by Hecht and Rothberger,<sup>1</sup> using quinidine upon the dog. Hoffmann,<sup>2</sup> who employed the excised and perfused dog's heart, noticed little change of rate, but Boden and Neukirch,<sup>1</sup> working with the perfused heart of rabbits and human foetuses, saw slowing.

*Effect on A-V conduction.* Schott and Hecht and Rothberger have observed depressed A-V conduction under quinidine and quinine, respectively: we also find a conspicuous effect under quinidine. A lengthened P-R interval is constantly manifested, even when the heart is allowed to beat naturally, but is best displayed and the measurements are more comparable when a uniform rate of beating (circa 200) is maintained. In the last circumstances dropped beats of the ventricle occur after total doses of 0·15 to 0·3 gramme have been given. It is to be stressed that the lengthened intervals are seen after each injection, whether the auricle is responding to a high rate of rhythmic shocks, or whether it is beating more slowly in response to its inherent impulses. The appearance of block, or the increase of pre-existing block, seems to take place irrespective of the rate of the auricle, though naturally the degree of block is greater when the auricle is beating rapidly. Recovery of the A-V conduction is simultaneous with recovery in the rate of the S-A rhythm.

Both in respect of the S-A rhythm and of A-V conduction, the height of the reaction is usually reached some two or three minutes after the actual injection, though occasionally it is delayed for a longer while (see Table V, Dogs NK and NL).

\* 0·1 gramme of quinidine sulphate was dissolved in 30 c.c. of warm normal saline.

† Though our doses far exceeded ours.

*Inter-intrinsic intervals.* These intervals, measured in the curves from contacts which remain stationary throughout the experiment, are used as an index of conduction in the auricle. The intervals tabulated (Tables I and II) for any given experiment apply to the auricle driven at a constant rate (circa 200). The quinidine injections invariably raise these intervals whether the auricle is atropinised or not. A rise of as much as 50 or even 100 per cent. may occur at the first injection of 0.1 gramme of the drug. Repeated injections increase this rise, though it rarely surpasses 100 per cent. altogether, and eventually the auricular curves become very irregular: this irregularity we ascribe to the presence of intra-auricular block. Progressive increase of the auricular conduction defect, and recovery, take place hand in hand with similar changes in auriculo-ventricular conduction.

These changes in auricular conduction are described for the first time, and this action of the drug is one of peculiar interest to therapeutics. Apart from noting that it is a direct action on the muscle, its discussion will be reserved to a later stage of this article, as will also the nature of the disturbance.

*Changes in the ventricular electrocardiogram (lead I I).* In a number of animals the length of the *Q.R.S.* group of deflections has been measured: the values obtained may be regarded as giving indices of intra-ventricular conduction, for the duration of the *Q.R.S.* group of deflections is a sufficiently close measure of the time taken for the excitation wave to spread throughout the ventricle. With quinidine these deflections are invariably lengthened, as our tables show, and, generally speaking, the values rise and fall hand in hand with the *P-R* values and the auricular conduction intervals. The rise in the values of the *Q.R.S.* group is about 20 or 30 per cent. after single doses of 0.1 gramme of quinidine: with repeated doses it rises 50 to 70 per cent. above its original value. Thus the measures of conduction in auricle, ventricle and at *A-V* conduction, show that quinidine exerts a seemingly uniform effect on the power of the several structures concerned in conduction.

So far as the direction and amplitudes of ventricular deflections are concerned, the chief change is in the end deflection *T*. Like Hecht and Rothberger<sup>1</sup> and Schott,<sup>12</sup> we notice usually an increase in the amplitude of *T* when the heart is allowed to beat naturally. That this is not an effect of changed heart rate is shown by the curves taken from the heart beating at a constant rate (circa 200). In these the changes in *T* are more conspicuous (see Fig. 1). Thus of five animals, in one, a *T* deflection, originally inverted, became upright and increased in amplitude: in three animals in which *T* was originally upright, it grew in height progressively. In one animal only (*Dog N H*) an originally inverted *T* was not influenced appreciably. There is no difference in the action according to whether the animal is atropinised or not.

*Absolute refractory period and threshold of excitability.* Hoffmann<sup>5</sup> states that the excitability of the auricle is much reduced by quinidine. He bases this statement upon his observation that it reacts less readily to induced shocks, and because he is unable, subsequent to perfusion of the heart with quinidine, to throw the auricle into a state of fibrillation by means of the faradic current. These observations had been made previously by Hecht and Rothberger, working with the intact dog. We are able to confirm these workers in their conclusions. Hecht and Rothberger have also seen long lasting fibrillation of the auricles promptly terminated in the dog by the drug, an observation which confirms what is now the well-known clinical action of the drug. We have also seen the same effect, fibrillation of the dog's auricle being almost at once abolished after it had persisted for thirty-five minutes. Hecht and Rothberger attribute these effects to diminished excitability.

To test the excitability of the auricle under quinidine we have used rhythmic shocks at a fixed rate, noting the distance at which the secondary coil must be placed from the primary for the heart to respond. The threshold value for cycles of a given length (auricular rate circa 200) is ascertained. It seems to be invariable that this threshold value of the exciting current is raised by quinidine injections: usually this effect goes hand in hand with the other actions of the drug. When recovery is noted in the rate of the S-A rhythm and in A-V conduction, there is a lessening of the threshold value (expressed in our table as a greater distance between the two coils): there are, however, minor exceptions to this rule.

There appears to have been no attempt on the part of the workers cited to analyse what they term lowered excitability. We have turned our attention to one factor, namely, the length of the absolute refractory period. These have been taken by the method described in a previous article<sup>8</sup> and are probably accurate within a few thousandths of a second. They apply to auricular rates of fixed value (circa 200 per minute). Our findings are given in the last column but one of Table II, and the times at which they were obtained are given immediately below each value.

The length of the refractory period at various stages of quinidine poisoning seemed of such theoretical consequence that no pains have been spared in testing it. The observations are confined to atropinised dogs, for in these only do the values accurately express the changes. The complete measurements, from which these values of Table II are compiled are given in Table III. Table III contains also the results in two preliminary experiments. The testing shocks, used in all these experiments were exclusively break shocks. In the first three experiments we were content to note the threshold point of this testing coil and to raise the strength of the shocks considerably when using it to estimate the refractory period. In later experiments the threshold point of the coil was tested before each series of observations upon refractory period was undertaken, and when considered advisable the strength of the testing shocks was raised, so that

it always lay very greatly above threshold value. In the last three experiments (*Dogs N H, N I and N J*) observations upon the refractory period were made at the same stage of quinidine poisoning, with the secondary coil at two points, both of which should, in our opinion, give the time value of the absolute period, and which actually proved to do so. Thus full precautions have been taken to obtain a measure of the absolute period, rather than of a period ending at some indefinite point in the phase of the relative refractoriness. When the coil has been used at two points (in the three experiments named) the estimated values of the absolute refractory period have been sufficiently close together. In one experiment only (*Dog N I*) was there a falling off of value when the strength of the shocks was raised (the value being 0.165 with the coil at 6 cm., and 0.148 when it was at 2 cm.). This reduction of refractory period is to be attributed to an actual change in the condition of the muscle: it was recovering, as the simultaneous rise of *S-A* rate and reduction of *P-R* interval (see Table II) clearly indicated.

Reviewing the values of Table II, it is apparent that quinidine in the doses employed lengthens the absolute refractory period considerably.\* The total rise varies between 50 and 100 per cent., the longest value seen being 0.193 of a second. In so far as may be judged, the change happens *pari passu* with the remaining manifestations. When the values of the refractory periods and the threshold values at the end of the cycles during rhythmic stimulation are compared, it seems to us that the greater part, if not the whole of the changed excitability in the auricle under quinidine, may be attributed to the lengthening of the refractory period, for the rise in the threshold values is relatively slight. It does not seem as though quinidine materially affects the rate at which excitability recovers. The significance of this rise in the refractory period from the standpoint of auricular fibrillation and its treatment with quinidine is deferred for discussion at the end of this article.

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\* A lengthening of the refractory period under quinidine has been surmised by several writers, but the basis of the supposition is not fully apparent to us.

TABLE I.  
*Quinidine sulphate. Untempered dogs.*

Dog & M. (kilo 9-6)	Record No.	Time.	Normal rhythm.			Rhythmic stimulation.		
			Rate.	P-R interval.	Rate.	P-R interval.	Inter-auric interval.	Threshold count.
Dog A M. (kilo 9-6)	1, 2 & 3	11 10 16'	141	0.078	195	0.084	0.0019	0.0079
	8, 9 & 10	11 21'	Quinidine sulphate 0.1 gr.					28.5 cm.
	11 28 30'	151	0.096		192	0.116	0.0123	0.0199
	18, 19 & 21	11 46 18'	132	0.093	192	0.111	0.0097	27.0 cm.
	23, 24 & 25	12 6 8'	144	0.101	193	0.116	0.0097	26.0 cm.
	12 163'	Quinidine sulphate 0.1 gr.						26.0 cm.
	32 & 33	12 21 23'	83	0.165	193	crystallised crushed test		0.0646
Dog A N. (kilo 9-8)	3, 4 & 5	11 34 12 16'	191	0.090	233	0.096	0.0106	0.0149
	17, 18 & 19	12 11'	Quinidine sulphate 0.1 gr.					29.0 cm.
	12 17 19'	159	0.099		232	0.151	0.0151	0.0672
	28, 29 & 30	12 46 47 1/2'	160	0.096	232	0.119	0.0147	26.5 cm.
	12 54'	Quinidine sulphate 0.05 gr.						26.2 cm.
	38, 39 & 40	1 0 1 2'	139	0.114	235	0.188	0.0173 or 1 (0.0241)	26.0 cm.
	1 6'	Quinidine sulphate 0.05 gr.						
Dog A K. (kilo 13-2)	46, 47 & 48	1 12 15'	131	0.112	235	0.237	Infra-auricular block	23.5 cm.
	1, 2 & 3	10 55 58'	190	0.080	211	0.088	0.079	0.0157
	13, 14 & 15	11 30 33'	116	Nodal rhythm	207	0.103	0.0119	0.0573
	11 33'	Quinidine sulphate 0.1 gr.						
	17, 18 & 19	11 43 16'	106	0.098	207	0.123	0.0196 ?	0.0653
	1, 2 & 3	11 25 27'	155	0.080	187	0.083	0.0067	0.0161
	8, 9 & 10	11 47 49 1/2'	123	0.091	187	0.106	0.0120	0.0572
Dog A L. (kilo 9-15)	18, 19 & 20	12 5 7'	82	0.126	185	one normal dropped beat	Infra-auricular block	25.5 cm.
	25, 26 & 27	12 13 45'	73	0.119	187	0.237	0.0153	26.5 cm.
	32, 34 & 35	1 9 11'	161	0.092	183	0.104	0.0134	
	1 15'	Quinidine sulphate 0.05 gr.						
	40, 41 & 42	1 21 23 1/2'	78	0.108	187	0.208	0.0166	21.0 cm.
	1 30'	Quinidine sulphate 0.05 gr.						21.0 cm.
	46, 47 & 48	1 33 35'	61	0.115				19.5 cm.
	52, 53 & 54	1 52 58'	60	0.116	182	dropped beat	Infra-auricular block	0.0798
	56, 57 & 58	2 1 51'	72	0.119	187	one normal dropped beat	Infra-auricular block	0.0702
	60, 61 & 63	2 18 21'	82	0.107	183	0.208	0.0114	21.0 cm.
					183	0.191	0.0109	



	Record No.	Time.	Normal rhythm.		Rhythmic stimulation.			
			Rate.	P-R interval.	Rate.	P-R interval.	Interic interval.	Q-R-S group.
Dog N G (kilo 9-7)	17, 18 & 19	12 25-28' 12 53' Quinidine sulphate 0.1 gr. 1 0-5'	135	0.100	208	0.102	0.0183	0.0404
	20, 21 & 22	1 0-5' 1 15' Quinidine sulphate 0.1 gr. 1 25-26'	120	0.107	208	0.132	0.0211	0.0505
	34, 35 & 36	1 25-26' 2 6' Quinidine sulphate 0.05 gr. 2 18-20'	90	0.125	208	0.192	0.0264	0.0544
	56, 57 & 58	2 18-20'	90	0.129	208	2:1 response	0.0389	—
	69 & 70	2 31-33'	90	0.122	200	0.181	—	0.0510
Dog N H (kilo 17)	12, 13 & 14	11 46-53'	160	0.093	214	0.104	0.0090	0.0492
	15, 16 & 17	11 55' Quinidine sulphate 0.15 gr. 12 4-8'	157	0.099	214	0.118*	0.0112	0.0553*
	12 31'	Quinidine sulphate 0.1 gr.	132	0.106	214	(2:1 block)	0.0155	0.0584*
	26, 27 & 28	12 40-42'	132	0.106	214	0.127*	—	—
						(2:1 block)	—	—
Dog N I (kilo 12-2)	13, 14 & 15	11 35-40'	156	0.092	187	0.094	0.0143	0.0449
	16, 17 & 18	11 44' Quinidine sulphate 0.1 gr. 11 55-57'	150	0.109	187	0.126	0.0170	0.0559
	12 33'	Quinidine sulphate 0.1 gr.	124	0.127	171	0.157	—	0.0624
	31, 32 & 33	12 40-43'	124	0.127	171	0.157	—	0.0624
	50, 51 & 52	1 0-4'	115	0.115	184	0.138	—	0.0630
Dog N J (kilo 10-5)	14, 15 & 16	11 35-37'	182	0.091	240	0.104	0.0118	0.0463
	17, 18 & 19	11 43' Quinidine sulphate 0.1 gr. 11 52-56'	175	0.100	234	0.108	0.0125	0.0528
	20, 30 & 31	12 5-8'	171	0.096	234	0.112	0.0170	—
	32, 33 & 34	12 17-20'	158	0.105	237	0.114	0.0155	—
	54, 55 & 56	12 51-54'	154	0.101	234	0.107	0.0131	0.0578
75, 76 & 77	1 18'	Quinidine sulphate 0.1 gr.	114	0.122	217	Prospect dropped beats	0.0192	0.0715
	1 33-36'							

\* Ventricular beating at half rate.



TABLE III.

*Refractory period before and after quinidine sulphate. (Atropinised anæsthetic.)*  
*Tested by means of break shocks.*

	Dog N C (kilo 9.5).			Dog N F (kilo 12.5).			Dog N G (kilo 9.75).				
	After (gr. total)			After (gr. total)			After (grammes total)				
	Before	0.05		Before	0.10 0.20		Before	0.10	0.20	0.20	0.25
	206	210	210	186	186	186	202	201	207	230	200
Auricular rate					0.244						
					0.205						
					0.199		0.168	0.194			
		0.306			0.191	0.237	0.157	0.165	0.208		
		0.223			0.180	0.228	0.152	0.160	0.195		
	0.445	<b>0.216</b>			0.176	0.214	0.143	0.160	<b>0.182</b>	0.224	0.212
	0.135	0.214	0.253		0.174	0.213	0.141	<b>0.146</b>	0.179	0.206	0.207
	0.134	0.208	0.234	0.186	0.165	0.212	0.132	<b>0.145</b>	0.173	0.197	0.203
	0.119	<b>0.208</b>	0.224	0.166	0.159	0.212	0.131	0.140	0.162	0.188	0.201
	0.114	0.199	0.215								
R.P.	0.109			<b>0.153</b>	<b>0.144</b>	<b>0.191</b>	<b>0.130</b>	<b>0.120</b>	<b>0.157</b>	<b>0.183</b>	<b>0.186</b>
		<b>0.104</b>	<b>0.186</b>	<b>0.122</b>	<b>0.111</b>	<b>0.186</b>	<b>0.118</b>	<b>0.112</b>	<b>0.120</b>	<b>0.166</b>	<b>0.178</b>
		<b>0.096</b>	<b>0.176</b>	<b>0.083</b>		<b>0.177</b>	<b>0.112</b>	<b>0.109</b>	<b>0.092</b>	<b>0.161</b>	<b>0.174</b>
		<b>0.092</b>	<b>0.159</b>			<b>0.175</b>	<b>0.109</b>	<b>0.099</b>	<b>0.084</b>	<b>0.152</b>	<b>0.166</b>
		<b>0.079</b>	<b>0.157</b>			<b>0.169</b>	<b>0.108</b>			<b>0.145</b>	
		<b>0.079</b>	<b>0.144</b>			<b>0.160</b>	<b>0.100</b>				
		<b>0.065</b>				<b>0.138</b>	<b>0.098</b>				
							<b>0.088</b>				
							<b>0.082</b>				
Coil at	8 cm.*	8 cm.	8 cm.	1 cm.	1 cm.	1 cm.	6 cm.	6 cm.	6 cm.	6 cm.	6 cm.
Thresh- old at	13 cm.			13 cm.			13.5 cm.				

	Dog N H (kilo 17.3).				Dog N I (kilo 12.2).				Dog N J (kilo 10.5).				
	After (grammes total)				After (grammes total)				After (grammes total)				
	Before	0.15	0.25	0.25	Before	0.10	0.20	0.20	Before	0.10	0.20	0.20	0.30
	208	212	204	204	186	187	188	188	223	235	238	236	212
Auricular rate													
			0.212										
			0.193										
			0.187	0.199	0.172						0.188		0.224
			0.179	0.196	0.149						0.185		0.208
	0.180		0.173	0.195	0.124	0.147	0.210	0.185			0.179	0.183	0.198
	0.166	0.181	0.173	0.195	0.124	0.147	0.210	0.185			0.170	0.178	0.181
	0.147	0.174	0.171	0.192	0.123	0.143	0.194	0.184			0.148	0.169	0.176
	0.147	0.174	0.171	0.192	0.123	0.143	0.194	0.184			0.148	0.169	0.176
	0.132	0.164	0.163	0.182	0.102	0.142	0.179	0.161	0.126	0.148	0.168	0.175	0.191
R.P.	0.130	0.154	<b>0.161</b>	<b>0.161</b>	<b>0.098</b>	0.139	0.175	0.156	0.124	0.144	0.167	0.171	0.187
	0.119	0.149	<b>0.158</b>	<b>0.161</b>	<b>0.096</b>	0.137	0.172	0.155	0.121	0.133	0.166	0.164	0.182
	0.112	0.143	0.151	0.159	0.093	0.133	0.171	0.150	0.119	0.132	0.165	0.163	0.167
	<b>0.109</b>	<b>0.140</b>	<b>0.144</b>	<b>0.142</b>	<b>0.077</b>	<b>0.115</b>	<b>0.159</b>	<b>0.146</b>	<b>0.100</b>	<b>0.121</b>	<b>0.156</b>	<b>0.149</b>	<b>0.157</b>
	<b>0.101</b>	<b>0.135</b>	<b>0.139</b>	<b>0.133</b>	<b>0.070</b>	<b>0.114</b>	<b>0.149</b>	<b>0.145</b>	<b>0.075</b>	<b>0.105</b>	<b>0.149</b>	<b>0.147</b>	<b>0.153</b>
	<b>0.100</b>	<b>0.135</b>	<b>0.133</b>			<b>0.112</b>	<b>0.137</b>	<b>0.143</b>	<b>0.068</b>	<b>0.104</b>	<b>0.144</b>	<b>0.136</b>	<b>0.148</b>
	<b>0.097</b>	<b>0.130</b>	<b>0.114</b>			<b>0.101</b>	<b>0.118</b>	<b>0.141</b>	<b>0.059</b>		<b>0.139</b>	<b>0.130</b>	<b>0.132</b>
	<b>0.094</b>	<b>0.122</b>				<b>0.100</b>	<b>0.110</b>	<b>0.131</b>			<b>0.137</b>	<b>0.125</b>	
	<b>0.083</b>	<b>0.117</b>										<b>0.119</b>	
R.P.	<b>0.081</b>	<b>0.099</b>											
	<b>0.073</b>												
Coil at	6 cm.	6 cm.	4 cm.	1 cm.	6 cm.	6 cm.	6 cm.	2 cm.	4 cm.	4 cm.	2 cm.	4 cm.	2 cm.
Thresh- old at	13.5 cm.		7.5 cm.	7.5 cm.	19 cm.	15.2 cm.	14.2 cm.	14.2 cm.	9.7 cm.	12.5 cm.	9.5 cm.	9.5 cm.	11.7 cm.

\* The secondary coil begins to cover the primary coil at 9.0 cm.

NOTE. The times at which quinidine was given and at which the refractory periods were observed may be found by consulting Table II.

*Response of the ventricle under varying auricular rates.*

It is well known that when the auricular rate is raised to a sufficient level the ventricle fails to respond regularly to all the auricular contractions. When this happens, a rise of auricular rate is accompanied by a fall of ventricular rate. It is also known that many influences which tend to produce chronic *A-V* block enhance this effect and prolong its manifestation over a longer scale of rising rate. Thus, if in asphyxial block or in heart block by compression, the auricle is driven to a high rate of beating, a very advanced grade of block and a consequent and considerable fall of ventricular rate frequently occurs. The *A-V* block produced by quinidine is no exception to the general rule. When in patients the auricles are fibrillating and quinidine is administered, the rate of auricular beating falls materially; meanwhile the ventricular rate rises. The rise in ventricular rate is in part attributable to the fall in auricular rate.\* The observation is not remarkable: on the contrary, this reaction is anticipated from experience of other varieties of *A-V* block. On occasion, however, under quinidine, the relation of block to auricular rate is an exaggerated one: and this fact appears to us worthy of special note. A slight rise of auricular rate may produce long standstill of the ventricle. The most conspicuous instance of this phenomenon which we have witnessed is illustrated in the accompanying table, which summarises the effects of varying the rate of auricular beating between 200 and 267 per minute. At the former rate and under a total dose of 0.25 gramme of quinidine, the ventricle responded at half rate; a rise of auricular rate to 250 or 260 per minute was repeatedly accompanied by standstill of the ventricle.

TABLE IV.  
*A-V conduction at different auricular rates under quinidine.*

<i>Dog N H (kilo 17.3). Total quinidine sulphate 0.25 gr..</i>		
Record No.	Rate.	<i>A-V</i> conduction.
45	267	Standstill of ventricle.
46	247	8:1, 6:1, 4:1 block.
47	225	Ventricular rate 112; 2:1 block.
48	257	3:1 block.
49	250	Standstill of ventricle.
50	200	Ventricular rate 100; 2:1 block.
51	263	Standstill of ventricle.

\* A second factor will be noted at a somewhat later stage.

*Action of quinidine upon the vagi.*

Quinidine has a very distinct and invariable action upon the vagi. If the nerve is stimulated subsequent to injections of the alkaloid, the customary action is found to be reduced or abolished.

In estimating the effects of quinidine upon the vagus we have used as indices two inhibitory reactions, namely, the power of the vagus to depress conduction from auricle to ventricle, and its power to reduce the rate of the sino-auricular rhythm. The procedure has been as follows: The heart beats are recorded from a limb lead (lead II) and a simultaneous curve is taken directly from the auricular surface. In testing the effect of faradising the vagus upon *A-V* conduction, the auricle is driven at a constant speed of about 200 per minute by means of rhythmic break shocks: if the heart is permitted to control its own rate of beating the degree of the reaction is materially influenced by slowing of this rate under quinidine and by the vagus and an accurate comparison of the drug's effects on the vagus is not possible. Before the administration of the alkaloid, control curves are taken to observe the degree of block produced at a given strength of stimulation. The strength of stimulation used is one which will produce a conspicuous reaction upon the heart while it is uninfluenced by the drug. The vagi are cleaned throughout their length in the neck and stimulated as high up as possible. In most of our experiments control curves of the reaction of the sino-auricular rhythm to vagal stimulation have also been taken. For the latter effect we note the degree of auricular slowing: for the former we note the degree of block produced at the *A-V* junction and express it in our tables as a ratio between the rate of auricular and ventricular beating (3 : 1 block, 2 : 1 block, etc.) for successive cycles, or in the case of 1 : 1 response being maintained, by inserting the values of the *P-R* intervals before and during stimulation. In expressing these *P-R* values we have been at much pains to ensure relative accuracy, using the system of measurement previously described: in cases of doubt we refer to the curve taken direct from the auricle.

Our tables comprise observations upon eight animals.\* In the first (*Dog N K*) the action of the vagus upon *A-V* conduction was alone tested. Before the administration of quinidine, stimulation of both right and left vagus yielded a high grade of partial block between auricle and ventricle. The vagi were repeatedly stimulated 10 minutes after the injection of 0.1 gramme of quinidine sulphate, and they were now found to exert little or no influence upon *A-V* conduction, even when the strength of stimulation was increased.

In the second experiment (*Dog N L*) the procedure was similar, but the observations were more extensive. Five minutes after the first injection (0.1 gramme) the effect of vagal stimulation was found to be conspicuously

\* The tables are built up from actual records, but it has been our general habit to stimulate the vagus and observe the effects and to re-stimulate and record the changes. Thus the gross changes were observed in duplicate.

reduced though not abolished. A little later distinct recovery was noted and a second and similar injection was given. Within two minutes of the second injection the effect of the vagi on *A-V* conduction was found to be almost abolished, the only change being a slight and very temporary rise in the lengths of the *P-R* intervals. During the next hour (between 12 o'clock and 1 12') recovery was conspicuous; during this period we noted for the first time a paradoxical effect, namely, a decrease in the grade of block during and consequent upon vagal stimulation. Thus, in Record 23, a stable condition of 1:1, 2:1 response is seen to pass into one in which the ventricle responds regularly to each auricular systole. At 1<sup>30</sup>', recovery being almost complete, a third dose (0.05 gramme) was administered. This dose induced irregular response of the ventricle while the auricle was driven rhythmically at a rate of 185 per minute. One minute later no effect of vagal stimulation on *A-V* conduction could be detected. At 1<sup>47</sup> $\frac{1}{2}$ ' we tested the effect of right vagal stimulation upon the natural sino-auricular rhythm and observed a slight but definite slowing of the heart. A half minute later the right vagus was observed to decrease the degree of *A-V* block prevailing. During the remainder of the experiment the right vagus partially recovered its usual influence on *A-V* conduction.

In the third experiment (*Dog N M*) the effects on *A-V* conduction were alone studied. A minute after the first dose of quinidine the vagal effect on conduction was almost abolished (Records 6 and 7). A little later (Records 13 to 16) we observed an exceptional reaction. During stimulation conduction was uninfluenced; but immediately at the cessation of stimulation a high grade of block developed. This observation, otherwise standing by itself, was obtained repeatedly. After a second dose of quinidine, the right nerve gave no reaction, the left nerve appeared to yield a slight paradoxical effect.

In the remaining five experiments the effects of vagal stimulation upon *A-V* conduction and also upon the sino-auricular rhythm were investigated before quinidine was given. These experiments are in the main confirmatory of those already described; it will be sufficient perhaps to draw attention to special features of the corresponding tables. In the fourth experiment, during the control stage, right and left vagal stimulation (*Dog N X*, Records 8 and 9) repeatedly gave rapid re-excitation of the auricle; this was not seen after the first dose of quinidine had been given. After the first injection the left vagus exerted an effect on the sino-auricular rate, which was only just recognisable (Records 16 and 27). After the second injection this vagus exerted no action (Record 37).

The fifth experiment (*Dog N O*) illustrates partial recovery of the nerves. It also illustrates the paradoxical reaction, namely, a reduction in the degree of block at the *A-V* junction (Record 79), although at this stage of the experiment stimulation of the same nerve gave a slight but appreciable inhibiting effect upon the sino-auricular rhythm.

In the eighth experiment (Records 45 and 46, *Dog NQ*), the paradoxical effect was also seen, though it was but trifling, the *P-R* interval falling away by a few thousandths of a second. The last observations are to be emphasised more because they show clearly that while the vagi were incapable of *depressing* conduction at the *A-V* junction at this stage of quinidine poisoning, they were capable nevertheless of exerting a very decided influence in retarding the sino-auricular rhythm (Records 44 and 47). Similar observations (though here the paradoxical effect on *A-V* conduction was unquestionable) are found in Records 24 to 26, *Dog NX*.

*Summary and discussion of effects on vagi.* The most striking effect of quinidine upon the vagi is its parietic action: this action, though not uniform in degree from animal to animal, is invariable. It occurs when doses of the drug comparable to those used clinically are employed.\* The action follows almost immediately upon the injection. Recovery begins to occur sometimes as early as five minutes after the injection: it may be delayed to 15, 20 or even 40 minutes. The effects of the quinidine itself upon *A-V* conduction can be gauged and the rate of recovery can be ascertained from the *P-R* intervals of Table V.† in cycles preceding vagal stimulation: the degree in which the heart is still poisoned by quinidine may also be judged, though less accurately, from the rates of the sino-auricular rhythm at different stages of the experiments. On comparing these data with those relating to the effects of vagal stimulation, recovery seems to be simultaneous in nerve and muscle. But it seems clear to us that the poison does not first produce its full effect simultaneously. The vagi‡ are paralysed or paralysed almost at once after the injection: the full action on the muscle is often delayed by several minutes (see *P-R* intervals of *Dog NK*, Records 8 to 10; *Dog NL*, Records 16 to 22 and 45 to 50; *Dog NM*, Records 6 to 13, etc.). The vagal mechanism appears to be more sensitive to the poison than is the muscle when the drug is given in the doses which we employ.

We use the term paralysis with some hesitation, for although the usual action of the nerves on *A-V* conduction is often completely abolished, yet an action upon the sino-auricular rhythm is still displayed in most instances: only rarely does this action completely fail.

The difference in this respect, which is in many experiments quite emphatic, requires explanation. The poison discriminates. Does it discriminate between those sections of the vagal mechanism which connect with one or other node? Does it discriminate in its action upon the muscle

\* In our dogs doses of 0.05 and 0.1 gramme are equivalent to doses of 0.25 to 0.75 gramme in men of 50 to 75 kilos body weight.

† These *P-R* intervals were measured in the preliminary beats preceding vagal stimulation.

‡ When we speak of the vagi we do not wish to infer that it is the nerve trunk which is affected; we have not investigated the locality in which the poison acts, though it is evident that the action described is peripheral. Whether it is in the ganglia or nerve endings is a matter for further investigation.

of the two nodes? Or is the apparent discrimination due to the manner of its display, in the case of the *S-A* node as a depression of rhythm and in the case of the *A-V* node as a depression of conducting power? Both the first and second explanations appear to us to be unlikely, for the two nodes are homologous structures and are similarly and richly supplied by the vagi: we shall continue our discussion upon the assumption that the third explanation is the correct one.

Although it may be the rule that quinidine greatly reduces or abolishes the power of the vagus to depress conduction at the *A-V* junction, there are exceptional instances in which, after the administration of quinidine, vagal stimulation reduces the degree of block which is manifested at this juncture. This result of vagal stimulation is directly opposed to that invariably witnessed in the unpoisoned dog's heart. We consider it unprofitable to discuss the possibility of simultaneous escape of the stimulating current to sympathetic fibres: such an action appears to us to be placed out of court by the simultaneous reaction upon the sino-auricular rhythm and by the fact that reversal is seen, not when the vagi are at the height of poisoning, but when recovery is beginning in them. When the paradoxical action at the *A-V* junction is seen, the effect upon the sino-auricular node is under the same condition definitely inhibitory. We are therefore inclined to regard the action upon *A-V* conduction as inhibitory, though the actual result is an increased power to conduct. In regarding it to be inhibitory, however, we must remark that another possibility is not definitely excluded. A remarkable reversal of the vagal action upon the sino-auricular rhythm under nicotine and other poisons has been described by Dale, Laidlaw and Symons.<sup>7</sup> These workers have advanced much evidence to show that this reversal is due to accelerator fibres belonging to the vagus (as opposed to sympathetic accelerator fibres running with the vagus): and there are some analogies between the reversal which we obtain and that described by them. A paradoxical inhibitory effect on *A-V* conduction is one which we have deliberately sought in a number of distinct experiments: and the present example is capable of being explained in the manner suggested by one of us recently.<sup>7</sup> According to the hypothesis to which we refer, the inhibitory action of the vagus displays itself in the heart in two ways. On the one hand, it weakens and shortens the systolic process: the refractory period of the muscle is reduced and, as a consequence, the period during which recovery takes place is lengthened. This action of the vagus in lengthening the period of rest tends to increase the degree of recovery in those processes upon which the next beat of the heart depends. On the other hand, the vagus decreases the *rate* at which recovery occurs. There is a conflict between these opposing influences and in the case of *A-V* conduction it is the last which normally predominates. But, as has been shown, that is not the case where auricular muscle is concerned: in this last, reduction of the refractory period plays the more important rôle and consequently the usual action of the vagus, when it affects auricular conduction at all, is to increase its

TABLE V.

Dog No.	Record No.	Time.	Rate of nipples.	Ventricle response.	Vagus.	Coil at	Effect.
Dog N.P. (kilo 9.8) Vagus out.	7	12 10'	R. 251	1:1 ( $P, R$ 0.000)	Right	60	2:1, 2:1, 2:1, 1:1, 2:1, 2:1.
	8	12 12'	R. 257	1:1 ( $P, R$ 0.102)	Left	60	6:1 and rapid re-excitation.
	9	12 13'	R. 256	1:1 ( $P, R$ 0.009)	Right	60	7:1 and rapid re-excitation.
	10	12 14'	R. 251	1:1 ( $P, R$ 0.009)	Left	60	Slows to 42.
	11	12 5'	N. 180	1:1 ( $P, R$ 0.089)	Right	60	Slows to 42 and occasional beats blocked.
	12	12 7'	N. 187	1:1 ( $P, R$ 0.092)	Left	60	
	13	12 11'	Quinidine sulphate 0.1 gr.				
	14	12 13'	R. 256	1:1 ( $P, R$ 0.160)	Right	60	1:1 ( $P, R$ averages 0.161*).
	15	12 14'	R. 253	1:1 ( $P, R$ 0.155)	Left	60	1:1 ( $P, R$ averages 0.158*).
	16	12 15'	N. 154	1:1 ( $P, R$ 0.108)	Right	60	1:1 ( $P, R$ averages 0.109*), rate falls to 140.
	17	12 16'	N. 158	1:1 ( $P, R$ 0.106)	Left	60	1:1 ( $P, R$ averages 0.107*), rate 156.
	18	12 17'	R. 253	1:1 ( $P, R$ 0.121)	Right	60	1:1 ( $P, R$ falls to 0.118).
	19	12 18'	R. 256	1:1 ( $P, R$ 0.123)	Left	60	1:1 ( $P, R$ falls to 0.119).
	20	12 44'	N. 155	1:1 ( $P, R$ 0.098)	Right	60	1:1 ( $P, R$ 0.098), rate falls to 109.
	21	12 45'	N. 158	1:1 ( $P, R$ 0.096)	Left	60	1:1 ( $P, R$ 0.095), rate falls to 156.
Dog N.P. (kilo 10.5) Vagus out.	22	12 50'	R. 251	1:1 ( $P, R$ 0.123)	Right	60	Occasional dropped beats.
	23	12 51'	R. 251	1:1 ( $P, R$ 0.105)	Left	60	Occasional dropped beats.
	24	12 51'	Quinidine sulphate 0.05 gr.				
	25	12 56'	R. 234	1:1 ( $P, R$ 0.221)	Right	60	1:1 ( $P, R$ averages 0.219*).
	26	12 57'	R. 234	1:1 ( $P, R$ 0.228)	Left	60	1:1 ( $P, R$ averages 0.228*).
	27	12 58'	N. 130	1:1 ( $P, R$ 0.121)	Right	60	1:1 ( $P, R$ 0.121), rate falls to 115.
	28	12 59'	N. 135	1:1 ( $P, R$ 0.118)	Left	60	1:1 ( $P, R$ averages 0.120*), rate unaltered.
	29	1 6'	Quinidine sulphate 0.05 gr.				
	30	1 84'	R. 257	Occ. dropped beats	Right	60	Occasional dropped beats.
	31	1 10'	R. 257	Occ. dropped beats	Left	60	Occasional dropped beats.
	32	1 46'	N. 16	1:1 ( $P, R$ 0.253)	Right	240	2:1, 1:1, 1:1, 1:1, 1:1.
	33	1 46'	R. 190	1:1 ( $P, R$ 0.250)	Right	240	2:1, 1:1, 1:1, 1:1, 1:1.
	34	1 47'	R. 187	1:1 ( $P, R$ 0.250)	Left	240	3:1, 1:1, 1:1, 1:1, 1:1.
	35	1 53'	R. 211	1 beat in 7 missed	Right	60	Very occasional beats missed. (Block also reversed). This result obtained repeatedly.
	36	1 54'	N. 78	1:1 ( $P, R$ 0.129)	Right	60	Rate falls to 78.

\* No apparent change.

Record No.	Time.	Rate of nipples.	Ventricle response.	Vagus.	Coil at	Vagus stimulation. Effect.	
Dog N.P. (kilo 10.5) Vagus cut.	7	11 49'	R. 187	1:1 ( $P, R=0.128$ )	Left	60	6:1, 12:1.
	8	11 49'	R. 187	1:1 ( $P, R=0.126$ )	Right	60	6:1, 12:1.
	9	11 50'	N. 116	1:1 ( $P, R=0.108$ )	Right	60	Profound slowing and block, eventually rapid re-excitation.
10	11 53'	N. 118	1:1 ( $P, R=0.107$ )	Left	60	Slowing to 67 and block.	
11	11 56'	Quinidine sulphate 0.1 gr.					
12	11 57'	R. 187	1:1 ( $P, R=0.094$ )	Right	60	9:1, 9:1, 9:1, 9:1, 9:1.	



No. of Goods		Description of Goods		Quantity		Value		Remarks	
1	10	Wheat	1000 bushels	1000	1000	1000	1000		
2	20	Barley	2000 bushels	2000	2000	2000	2000		
3	30	Oats	3000 bushels	3000	3000	3000	3000		
4	40	Rye	4000 bushels	4000	4000	4000	4000		
5	50	Corn	5000 bushels	5000	5000	5000	5000		
6	60	Soybeans	6000 bushels	6000	6000	6000	6000		
7	70	Peas	7000 bushels	7000	7000	7000	7000		
8	80	Lentils	8000 bushels	8000	8000	8000	8000		
9	90	Beans	9000 bushels	9000	9000	9000	9000		
10	100	Flour	10000 bushels	10000	10000	10000	10000		
11	110	Wheat	11000 bushels	11000	11000	11000	11000		
12	120	Barley	12000 bushels	12000	12000	12000	12000		
13	130	Oats	13000 bushels	13000	13000	13000	13000		
14	140	Rye	14000 bushels	14000	14000	14000	14000		
15	150	Corn	15000 bushels	15000	15000	15000	15000		
16	160	Soybeans	16000 bushels	16000	16000	16000	16000		
17	170	Peas	17000 bushels	17000	17000	17000	17000		
18	180	Lentils	18000 bushels	18000	18000	18000	18000		
19	190	Beans	19000 bushels	19000	19000	19000	19000		
20	200	Flour	20000 bushels	20000	20000	20000	20000		



rate. It has been surmised that, in special circumstances, the refractory period factor might predominate in the case of the junctional tissues also: if that is so it would constitute an adequate explanation of the paradoxical phenomenon which we witness. It would also explain why under quinidine, the vagal effect on A-V conduction is often seemingly abolished, while the effect on the sino-auricular rhythm in some measure remains. At the A-V junction the balance between the opposing influences, such as we suppose to exist, is to be regarded as a nice one under quinidine, one or other influence slightly predominates and produces on one occasion depressed, on another enhanced conduction, and in yet another, the balance being equal, no effect is apparent.

The parietic effect of quinidine upon the vagi must influence in some measure the general reaction of the heart to quinidine. In observing the effects of quinidine upon the sino-auricular rhythm in our experiments we note, as other observers have done, a profound slowing: this, as we have seen, results from a direct action on the muscle: paresis of the vagi might be expected partially to counteract this effect and, when given to intact animals or man, this counter influence is very probably present: in the circumstances of our present experiments a counter influence is improbable, for the natural vagal tone becomes abolished early in the experiment after the opening of the pericardium. When quinidine is given to patients in whom auricular fibrillation is present it is customary to observe a quickened action of the ventricle: in part this quickening may be due to paresis of the vagi.

#### *After-effects of rhythmic stimulation on S-A rhythm under quinidine.*

If in dogs, in which the vagi are cut, the auricles are rhythmically stimulated at a high rate, on terminating the rhythmic stimuli the normal S-A rhythm is at once restored. For a few cycles this restored rhythm may be very slightly faster than before rhythmic stimulation or the two rates may be identical. Exceptionally and when the heart is in poor condition a slower rhythm of development may be seen, the S-A rate rising to its former value shortly after the end of rhythmic stimulation.<sup>11</sup> In similar circumstances, and under quinidine, a slower action of the S-A rhythm when rhythmic stimulation ceases is the rule. The accompanying table sufficiently illustrates the chief manifestations. Sometimes there is a gradual increase of rate for several cycles and until the original rate of beating is resumed: sometimes the first cycle of the restored rhythm is alone lengthened. The first cycle is always the longest, and it may be so long as to constitute standstill of the whole heart: in these circumstances the pause resembles that seen when an idio-ventricular rhythm is interrupted temporarily by rapid rhythmic shocks applied to the ventricle. In the ventricle this phenomenon has been ascribed by Cushman<sup>2</sup> to fatigue of the ventricular pacemaker. Presumably it is of similar origin in the auricle poisoned by quinidine: it seems important

to note, however, that it is not a normal reaction, but seems peculiar to an *S-A* node damaged by poison, or in some other way.

A similar slowing, or from time to time actual short standstill of the heart, may be anticipated in cases of auricular fibrillation, treated with quinidine, immediately at the restoration of the normal rhythm. Clinical records of the actual change have not as yet been taken.

TABLE VI.

*After effects of rhythmic stimulation on sinus rhythm under quinidine.*

	Record No.	Total quinidine.	Rate of stimulation.	Original length of sinus cycle.	Sinus rhythm recovering.		
					First cycle in secs.	Subsequent cycles in secs.	Length of restored normal cycle.
<i>Dog NM</i> (vagi cut)	20	0.1 gr.	194	0.45	0.48	0.43, 0.43, 0.43	0.45
	34	0.2 gr.	195	0.72	2.64	0.86, 0.86, 0.86	0.72
<i>Dog NX</i> (vagi cut)	21	0.1 gr.	230	0.38	0.50	0.38, 0.38, 0.38	0.38
	42	0.15 gr.	235	0.44	0.62	0.56, 0.54, 0.48, 0.48	0.43
	50	0.2 gr.	236	0.46	0.72	0.68, 0.52, 0.52	0.46
<i>Dog NO</i> (vagi cut)	71	0.3 gr.	207	0.57	0.72	0.64, 0.64, 0.64	0.64

Cycles measured from *P* to *P* summits.

*Further observations on conduction in the auricle under quinidine.*

It has been seen that, measured while the auricle is beating at a rate of 200 per minute, a lowered rate of conduction in the auricle is invariable when the muscle is poisoned by quinidine.

*Influence of rate.* It is next important to inquire how this delay in conduction is influenced by the rate of rhythmic stimulation. The observations of Table VII were made upon atropinised dogs from this point of view. It will be seen that, in so far as the values of this table are concerned, that the auricular rate of 200 is usually sufficiently representative. The rate of conduction is usually approximately the same for rates of 200 and such lower rates as can be obtained. The lowest rate obtainable is limited by the natural rate of the auricle. If higher rates than 200 are used, and occasionally when rates above 150 are used, the conduction interval is further prolonged until, at such low rates as 260 or 280, the auricle fails to respond to each stimulus entering it. The lengthening of the originally prolonged interval as the rate rises may be relatively abrupt and lead up

almost at once to intra-auricular block, or it may be gradual and progressive from a rate of 200 (exceptionally 150) onwards. Prior to the failure of response, the auricular curve shows conspicuous irregularity of its deflections; it is to this phenomenon that the term intra-auricular block is applied. All these events are quite parallel to those seen in the unpoisoned heart; but in the unpoisoned heart they occur at a much higher scale of rates (*i.e.*, 150 to 200 beats per minute higher). We do not hesitate to ascribe the final lengthening of intervals consequent upon a rise of auricular rate, to the stimuli entering muscle while it is in a partially or, at the highest rates, when responses are missed, in a wholly refractory state: for the refractory period of the auricular muscle has been raised 50 or 70 per cent. by the quinidine. But it is not clear that the constantly lengthened intervals at the lowest auricular rates can be ascribed to similar causes. If the relation of the impulses to the refractory period, absolute or partial, were the sole factor inducing altered conduction under quinidine we should anticipate that at the lowest rates conduction would not be altered materially, and that where very low rates of beating were obtainable, the conduction interval before and after quinidine would be unchanged. In point of fact we do not find that this is so (many examples of intervals at low rates of beating which support this statement will be found from Table IX).

*Influence of vagal stimulation.* The same problem has been approached in a different way. It may be remembered that when the conduction intervals become widened in the unpoisoned auricle purely in response to raised rate of beating, an event which occurs usually at a rate of about 350 or over, then these lengthened intervals can be reduced once more to normal by vagal stimulation.<sup>8</sup> This reduction under vagal stimulation has been used as an argument that the widened intervals result from the impulses reaching muscle in a partially refractory state: normally, vagal stimulation greatly shortens the refractory period, and consequently the impulses enter the muscle when it is in a more responsive condition. We have attempted to carry out the same experiment under quinidine. Table VIII contains those of our results which apply to auricular rates fixed at a constant level (circa 200) for given experiments. Now quinidine produces, as we have seen, paresis of the vagus, and consequently a full effect on the absolute refractory period is not to be anticipated; it is necessary in such experiments therefore to obtain an index of vagal activity, and for this we have relied chiefly, though not wholly, upon its simultaneous effect on the A-V junction. In the last column of our table we state the effect of vagal stimulation by comparing it with the normal effects. The right vagus was employed exclusively in these experiments.

The results are not precisely uniform, but in general it may be said that when the vagi are known to be acting, the widened conduction intervals, which prevail in the auricle beating under quinidine at a rate of about 200 per minute, are definitely, though slightly, reduced by vagal stimulation.

TABLE VII.

*Conduction is auricle (atropinised) under quinidine and at different rates of stimulation.**Dog N H (kilo 17.3). Total quinidine sulphate 0.25 gram. (dog well under quinidine).\**

Record No.	Rates.	Transmission interval.	Deflections.
45	262	Occasional failure of response.	—
54	230	0.0162	Irregular.
53	224	0.0154	Irregular.
55	210	0.0136	Very slight irregularity.
56	191	0.0129	Regular.
57	163	0.0123	Regular.
58	146	0.0137	Regular.
59	125	0.0148	Regular.
60	116	0.0142	Regular.

*Dog N I (kilo 12.2). Total quinidine sulphate 0.2 gram. (dog recovering from quinidine).\**

53	280	Occasional failure of response	—
53	280	0.0128	Regular.
56	222	0.0091	Slight irregularity.
57	193	0.0081	Slight irregularity.
58	138	0.0092	Regular.

*Dog N J (kilo 10.5). Total quinidine sulphate 0.3 gram. (Original interval 0.0118 at rate of 240).*

75	217	0.0192	Regular.
78	157	0.0172	Regular.

*Dog N U (kilo 8.3). Total quinidine sulphate 0.1 gram. (dog well under quinidine).\**

3	137	0.0194	Slight irregularity.
4	158	0.0194	Slight irregularity.
5	190	0.0190	Slight irregularity.
6	225	0.0210	Slight irregularity.
7	245	0.0251	Slight irregularity.
8	278	0.0267	Irregular.
9	322	Intra-auricular block	Very irregular.
10	155	0.0200	Slight irregularity.

*Dog N U (kilo 8.3). Total quinidine sulphate 0.2 gram. (dog well under quinidine).\**

11	79	0.0243	Regular.
12	110	0.0246	Very slight irregularity.
13	140	0.0226	Very slight irregularity.
14	158	0.0307	Regular.
15	182	0.0369	Regular.
16	205	0.0365	Slight irregularity.
17	230	0.0430	Irregular.
18	272	2:1 response	—
19	107	0.0262	Slight irregularity.

\* The original conduction intervals (before quinidine) cannot be given for these animals, as the recording contacts had been moved before the curves on which the present table is based were taken; but the values given for rates of about 190 may be taken as already raised 50 per cent. or more by quinidine.

TABLE VIII.  
Effect of cold rectal stimulation on the peripheral conduction in the carotid under quinidine sulphate.

	Record No.	Total amount of quinidine in grams.	Arricular rate.	Inter-atrial intervals during vagal stimulation.	ECG.	Simultaneous vagus-effect, on J-P conduction.
<i>Dog N K</i> (kilo 13-2)	15 & 16 17 & 20	0.1 0.2	207 207	0.0119 0.0106	0.0167 0.0167	Probably none. Probably none.
<i>Dog N L</i> (kilo 34-1)	1 10 & 11 20 & 21	0.0 0.1 0.2	188 187 188	0.0097 0.0120 0.0120	0.0091 0.0091 0.0091	Less than normal but very distinct. Less than normal but very distinct. Less than normal but very distinct.
	32	(recovery)	187	0.0123	0.0140	Less than normal but very distinct.
	42 & 43	0.2 0.2 0.30	183	0.0134	0.0130	A little less than normal.
	48	(recovery)	185	Inter-atrial color black, reduced.	0.0130	Reverse of normal, block decreased.
	63 & 64	0.30 0.20 (recovery)	187	Inter-atrial color black, reduced.	0.0130	Less than normal but distinct.
			182	Inter-atrial color black, reduced.	0.0119	Vagus suspected of failing.
<i>Dog N M</i> (kilo 9-6)	3 11 & 12 21 & 22	0.0 0.1 0.1	195 192 194	0.0049 0.0052 0.0057	0.0098 0.0098 (alternating)	None. None. Less than normal but very distinct.
	25 & 26	0.1 (stationary)	194	0.0057 0.0057	0.0080 (alternating)	Less than normal but very distinct.
<i>Dog N N</i> (kilo 8-8)	3 19 & 20 30 & 31	0.0 0.1 0.1	233 232 232	0.0106 0.0134 0.0147	0.0117 0.0134 0.0172	None. None. Less than normal but distinct.
	40 & 41	0.15 (recovery)	235	0.0173	0.0234	Less than normal but distinct.
	48 & 49	0.2	235	Inter-atrial color black, slightly reduced.	0.0241	None.
<i>Dog N O</i> (kilo 12-3)	7 11 & 13 21, 22 & 23	0.0 0.1 0.1	210 210 210	0.0138 0.0183 0.0226	0.0191 0.0203 0.0250	Much less than normal but distinct. Somewhat less than normal.
	31, 32 & 36	0.2	210	0.0229	0.0249	Much less than normal but distinct.
	43 & 44	0.25 (recovery)	210	0.0226	0.0267	Much less than normal but distinct.
	52 & 53	0.25 (recovery)	212	0.0261	0.0192	Somewhat less than normal.
	56 & 57	0.30 (recovery)	210	0.0304	0.0241	Less than normal but distinct.
	64 & 65	0.30 (recovery)	216	0.0250	0.0243	Much less than normal but distinct.
<i>Dog N P</i> (kilo 10-5)	1 16 & 17	0.0 0.1	189 189	0.0081 0.0126	0.0113	Much less than normal but distinct.
<i>Dog N Q</i> (kilo 9-9)	3 7 & 9 27 & 28	0.0 0.1 0.1	174 178 167	0.0043 0.0059 0.0083	0.0098 0.0074	Less than normal but distinct.
	40 & 41	0.20 (recovery)	180	0.0109	0.0107	Less than normal but distinct.
<i>Dog N R</i> (kilo 8-15)	3 7 16 & 17	0.0 0.1 0.1	200 200 196	0.0106 0.0160 0.0130	0.0140 0.0144	Less than normal but distinct.
	33 & 34	0.15 (recovery)	186	0.0168	0.0126	Less than normal but distinct.
	51 & 52	0.2	198	0.0197	0.0165	Less than normal but distinct.



TABLE IX.

*Conduction in auricle (undrugged) under quinidine, at different rates of rhythmic stimulation and before and during vagal stimulation.*

Record No.	Auricular rates.	Transmission intervals.		Simultaneous effect of vagus on A-V conduction, etc.
		Before.	During vagal stimulation.	
<i>Dog NX (kilo 98). Total quinidine 0.2 grammes (original interval 0.0106 sec. at rate 233).</i>				
53 & 54	139	0.0127	0.0131	No apparent effect on A-V conduction, but slight slowing of normal rhythm.
55	175	0.0124		
56 & 57	203	0.0145	0.0132	P-R very slightly lengthened. Slight slowing of normal rhythm.
58	219	0.0140		
59 & 60	249	0.0162	0.0142	No apparent effects.
61 & 62	280	0.0135 or 1.0.0158	0.0126	No apparent effects.
<i>Dog NY (kilo 123). Total quinidine 0.25 grammes (original interval 0.0138 sec. at rate 210).</i>				
43 & 44	210	0.0226	0.0207	Dropped beats of ventricle.
45, 46 & 47	121	0.0182	0.0186 or 1.0.01865	Widened P-R intervals.
48 & 49	159	0.0209	0.0197	Widened P-R intervals.
50 & 51	180	0.0202	0.0192	Widened P-R intervals.
52 & 53	212	0.0210	0.0192	Widened P-R intervals.
<i>Dog NY (kilo 123). Total quinidine 0.30 grammes (original interval 0.0138 sec. at rate 210).</i>				
56 & 57	210	0.0304	0.0241	Slight slowing of normal rhythm.
58 & 59	112	0.0241	0.0207	P-R slightly prolonged. Slight slowing of normal rhythm.
60 & 61	132	0.0223	0.0198	P-R unchanged, distinct slowing of normal rhythm.
62 & 63	155	0.0216	0.0205	P-R unchanged, distinct slowing of normal rhythm.
64 & 65	216	0.0250	0.0215	P-R unchanged, distinct slowing of normal rhythm.
66 & 67	107	0.0190	0.0171	Single dropped ventricular beat; normal rhythm slows distinctly.
<i>Dog NX (kilo 990). Total quinidine 0.1 grammes (original interval 0.0043 at rate 174).</i>				
7 & 9	179	0.0099	0.0091	Dropped ventricular beats.
10 & 11	187	0.0094	0.0087	Prolonged P-R intervals.
12 & 13	207	0.0101	0.0087	Dropped ventricular beats.
14 & 15	220	0.0112	0.0100	Dropped ventricular beats.
16 & 17	230	0.0122	0.0122	Prolonged P-R intervals.
18	200			

Year	Month	Day	Time	Location	Remarks
1988	00	188	0000	0000	0000
1989	00	195	0000	0000	0000
1990	00	202	0000	0000	0000
1991	00	210	0000	0000	0000
1992	00	217	0000	0000	0000
1993	00	224	0000	0000	0000
1994	00	231	0000	0000	0000
1995	00	238	0000	0000	0000
1996	00	245	0000	0000	0000
1997	00	252	0000	0000	0000
1998	00	259	0000	0000	0000
1999	00	266	0000	0000	0000
2000	00	273	0000	0000	0000
2001	00	280	0000	0000	0000
2002	00	287	0000	0000	0000
2003	00	294	0000	0000	0000
2004	00	301	0000	0000	0000
2005	00	308	0000	0000	0000
2006	00	315	0000	0000	0000
2007	00	322	0000	0000	0000
2008	00	329	0000	0000	0000
2009	00	336	0000	0000	0000
2010	00	343	0000	0000	0000
2011	00	350	0000	0000	0000
2012	00	357	0000	0000	0000
2013	00	364	0000	0000	0000
2014	00	371	0000	0000	0000
2015	00	378	0000	0000	0000
2016	00	385	0000	0000	0000
2017	00	392	0000	0000	0000
2018	00	399	0000	0000	0000
2019	00	406	0000	0000	0000
2020	00	413	0000	0000	0000
2021	00	420	0000	0000	0000
2022	00	427	0000	0000	0000
2023	00	434	0000	0000	0000
2024	00	441	0000	0000	0000
2025	00	448	0000	0000	0000
2026	00	455	0000	0000	0000
2027	00	462	0000	0000	0000
2028	00	469	0000	0000	0000
2029	00	476	0000	0000	0000
2030	00	483	0000	0000	0000
2031	00	490	0000	0000	0000
2032	00	497	0000	0000	0000
2033	00	504	0000	0000	0000
2034	00	511	0000	0000	0000
2035	00	518	0000	0000	0000
2036	00	525	0000	0000	0000
2037	00	532	0000	0000	0000
2038	00	539	0000	0000	0000
2039	00	546	0000	0000	0000
2040	00	553	0000	0000	0000
2041	00	560	0000	0000	0000
2042	00	567	0000	0000	0000
2043	00	574	0000	0000	0000
2044	00	581	0000	0000	0000
2045	00	588	0000	0000	0000
2046	00	595	0000	0000	0000
2047	00	602	0000	0000	0000
2048	00	609	0000	0000	0000
2049	00	616	0000	0000	0000
2050	00	623	0000	0000	0000



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They are not reduced to the level obtaining before the poisoning, though this is very possibly due to the weakened vagal action. It is also found that when under the named condition, intra-auricular block appears, vagal stimulation tends to abolish it and that irregular deflections tend to give place to regular ones during the full effect of vagal stimulation.\* An exception to this rule was once seen, however, and is noted in the table: in the case of *Dog N M*, regular deflections gave place to alternating ones during the nerve stimulation.

Judging from these results, they seem to confirm the view that the lengthened intervals at relatively high rates of stimulation are at least in part conditioned by the time relations of the partially refractory period.

The auricular rates employed, however, were somewhat lower than those most suitable to test this question. Finding that vagal stimulation is capable of reducing the conduction intervals prevailing at these rates of stimulation, we examined its effect on the conduction intervals at different rates of beating in the later experiments and the results are shown in Table IX. This table also supplements Table VII, in showing the change of conduction interval relative to change of rate.

It seems in general to be true that when the auricle is driven rapidly and the conduction interval is conspicuously wide, vagal stimulation exerts its most conspicuous effect; and that at the lowest rates of stimulation, though the conduction interval is widened, vagal stimulation fails to influence it. It is not possible, however, to render this generalisation in a quite positive manner, for there have been a few exceptions in which at lower rates of stimulation vagal stimulation has seemed still to reduce the intervals a little (notably in *Dog N O*, Records 60 and 61, *Dog N R*, Records 24 and 25). In so far as the rule is applicable it supports our contention that the largest intervals, *i.e.*, those prevailing at rapid rates, are largely the result of the partial refractory period factor, while it also supports our *suggestion* that the long intervals prevailing at lower rates of beating are differently occasioned. The presence of two factors has to be considered: the one is consequent upon rate and is but an early manifestation of a similar event in the unpoisoned heart; the other appears to be unrelated to rate, though the manner in which the drug produces this retarded conduction is not yet clear to us.†

\* In the initial stage of vagal stimulation the irregularity may be increased.

† It is conceivable that quinidine brings a proportion of the fibres of the auricle to rest and that even the conduction change at low rates is engendered by partially refractory muscle: but we hesitate at present to accept this as an explanation.

*Discussion on the action of quinidine upon the fibrillating auricle.*

When quinidine is administered to patients suffering from auricular fibrillation the chief reactions observed are three in number; they are: (1) a progressive decrease in the rate of the oscillations produced in the auricle, (2) sudden ending of the abnormal auricular mechanism and a return of the normal heart rhythm, and (3) an increase of the ventricular rate while the auricular oscillations are slowing.

It has been the object of the present investigation to throw light on these manifestations. The first and second may be considered together.

*1 and 2. Change in the auricular action.* Our views as to the mechanism of the fibrillating auricle have been recorded recently in a number of papers to this Journal. We have put forward, as we think, abundant evidence to show that fibrillation of the auricles is due fundamentally to a simple circus movement in the auricle.

Emphasis has been laid on two main points, namely, the length of the refractory period of the auricle and the rate of conduction in the auricular muscle, and their values in auricular flutter have been discussed at some length.<sup>8</sup> More recently one of us<sup>6</sup> has summed up our conclusions and re-emphasised the importance of studying the refractory period and rate of conduction in relation to flutter and fibrillation.

In fibrillation, according to this view, the excitation wave circulates continuously in the auricle, re-entering the same or much the same path over and over again. It is able to re-enter because a sufficient time elapses between one circuit and the next to permit recovery. There is always a short gap of responsive muscle between the crest of the travelling wave and the wake of its retreat. Re-entry is possible only if, on the one hand, the rate of conduction is sufficiently slow and, on the other hand, the refractory period at any given point is sufficiently short. If the refractory period is long then the crest of the travelling wave will be unable to re-enter, for it will find the muscle in front of it unresponsive; if conduction is rapid the wave will fail to re-enter because the circuit is completed so quickly that the muscle ahead of the advancing wave fails to recover in time to receive this wave again. Thus, if the conclusion that auricular fibrillation is a simple circus movement is correct, any agency which prolongs the refractory period sufficiently or quickens conduction sufficiently will bring the fibrillation to an end.

A lengthening of the refractory period will tend to close the gap between the crest of the advancing wave and the wake of retreat; if the gap actually becomes closed, re-entry upon the same path is clearly impossible. It does not necessarily follow that the circus movement will end, however, for it may then be deflected along a muscular path of greater circumference; but there must be a limit to this process, and sooner or later the wave will have no such option and circus movement will cease. Thus, a lengthened

refractory period, while the auricle fibrillates, will lead theoretically to one of two results, abrupt termination of the circus movement, or abrupt termination after a preliminary phase during which the circuit becomes larger. Widening of the circuit, conduction remaining unchanged, will decrease the number of revolutions per minute. If we administer a drug which, like quinidine, is known profoundly to lengthen the refractory period, the effects which we expect to obtain is an ending of the fibrillation, with or without a preliminary period of slowing in the oscillations of the auricle: for these oscillations, as has been shown, correspond to the circulation of the wave.<sup>9</sup>

When quinidine is administered in clinical fibrillation both the cessation of the fibrillation and slowing of the oscillations are seen. But the first phenomenon is inconstant and the second is invariable: cessation of the fibrillation does not occur without a preliminary phase of slowing.

We may with some confidence attribute the ending of the clinical circus movement to closure of the gap, consequent upon lengthening of the refractory period: we cannot with the same confidence assume that slowing of the oscillations is due to a lengthened refractory period and the deflection of the circulating wave upon a longer course. For, as has been shown, another factor is at work: quinidine slows profoundly the rate at which the wave travels. In doing so it widens the gap, and thus tends to establish the circus movement more firmly. At the same time, by slowing conduction, quinidine must exert a decided influence on the rate of the oscillations: the revolutions will be slower. Thus, there are two factors at work which may produce slower circus movement: of these the conduction factor will invariably produce slowing, the refractory period factor may do so if the conditions are suitable. Because slowing is invariable clinically, and because a lowered rate of conduction is invariable in our experiments, for these reasons and others, to be stated presently, we conclude that this change in conduction is the main factor, very probably in many cases the only factor, at work in producing slowing: but it is also to be acknowledged on theoretical grounds that a lengthened refractory period may at times produce a similar result. In cases where the rate of the auricular oscillations slow from 600 to 180 per minute, as they may do clinically under quinidine, it may be argued that it is scarcely conceivable that one or other factor is alone responsible. Assuming the gap in fibrillation to be extremely short, slowing of the circus movement to one third of its original value would necessitate a 300 per cent. increase in the refractory period, or a 300 per cent. increase in the length of time taken to travel. Increases of these magnitudes are not seen experimentally, and it is therefore probable that in these exceptional cases the two factors work together to produce slowing. It may be that experience will prove auricles, in which very profound grades of slowing are seen without resumption of the normal rhythm, to be of unusual size.

The effect of quinidine upon conduction has to be considered from another point of view. While a lengthened refractory period tends to close

the gap, a lowered rate of conduction tends to widen it. The two effects of quinidine are opposed in so far as they influence the termination or continuation of circus movement. While we attribute the frequent abolition of clinical fibrillation by quinidine to a predominant influence upon the refractory period, we attribute its equally frequent failure to end the fibrillation to its balancing or predominating influence on conduction.

If we may judge from our experiments, the balance is ordinarily a nice one, for while quinidine in full doses raises the refractory period by some 50 to 100 per cent., it raises the transmission intervals by similar quantities. An equal and simultaneous percentage increase of the two values would leave the length of the gap unchanged: it would leave the path taken by the wave unchanged, but would increase the circulation time correspondingly. Consideration will further show that only in those instances in which the percentage increase in the refractory period exceeds that in the transmission intervals must the circuit enlarge if the movement is to continue.

To sum up, the action of quinidine upon the auricle is two-fold: it lengthens the absolute refractory period, it slows conduction in the auricle. These two ascertained actions fully explain the action of quinidine upon clinical fibrillation of the auricle, providing that the theory of fibrillation which we support, namely, that this disorder of the auricle is fundamentally a circus movement, is accepted.

3. *Ventricular acceleration.* The meaning of this clinical phenomenon has been discussed already. There are two reasons why the responses of the ventricle to the fibrillating auricle should increase in number. The first is the lowering of the auricular rate, the second is the paresis of the vagus. The part played by one or other cannot be judged from our experiments: this question is one more open to clinical investigation and explanation.

#### SUMMARY AND CHIEF CONCLUSIONS.

1. Quinidine sulphate, given to dogs, in doses comparable to those used clinically, has the following effects:—

- (a) It lowers the *S-A* rate considerably.
- (b) It reduces the rate of conduction in auricle and ventricle: it depresses *A-V* conduction. The influence of the drug appears to be relatively uniform in the three tissues involved.
- (c) It lengthens the absolute refractory period of the auricular muscle.
- (d) It causes a partial, rarely a complete, paralysis of the vagus.

2. The first three of these effects result from a direct action in the muscle: they are produced simultaneously and are recovered from simultaneously. The full effect on the vagus somewhat precedes the full effect on the muscle, but recovery happens simultaneously with recovery in the muscle.

3. The nature of the action of quinidine upon conduction in the auricle is discussed. In large part it appears to be independent of the rate of beating: at higher rates of beating it is reinforced by the partially refractory period factor.

4. A curious reversed action of the vagus upon A-V conduction is described as happening under quinidine.

5. The effects of quinidine sulphate upon clinical fibrillation of the auricle are explained, if the last is regarded as fundamentally due to circus movement. A sufficient lengthening of the refractory period, by reducing the responsive gap, will either bring the circus movement to an end or it will slow the circuit movements. A reduced rate of conduction will slow the circuit movements, but will tend to establish the circus movement more firmly. If the refractory period factor predominates, the circus movement will end: if the conduction factor predominates, the circus movement will not end, but will become slower.

An increased rate of ventricular beating under quinidine, in auricular fibrillation, is ascribed to the lowered rate of auricular beating in part, and to paresis of the vagi in part.

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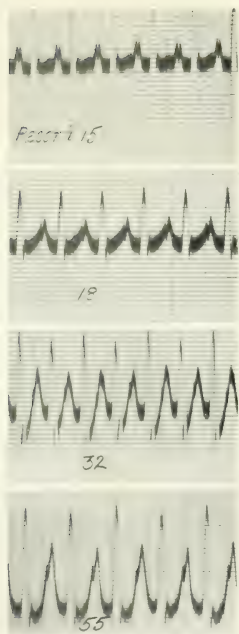


FIG. 1. *Day X I, Records 15, 18, 32 and 55, respectively.* Each curve is from lead *II*, and the heart is beating in response to rhythmic shocks of almost constant rate (234 to 240 per minute), applied to the auricular appendix. *Record 15* after atropine and before quinidine; *record 18* ten minutes after 0.1 gram quinidine sulphate; *record 32*, eight minutes after a second and similar dose; *record 55*, forty-three minutes after the second dose.

There is a progressive increase in the height of the *T* wave. There is a slight increase in the *P-R* and *Q-R-S* intervals, see Table II.



NOTE ON THE REVERSAL OF VAGUS ACTION BY QUINIDINE,  
AS SEEN IN THE HEART OF THE CAT.

By H. H. DALE.

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My colleagues at the University College Hospital Medical School have shown me the records in which an apparent reversal was observed, of the normal effect of vagus stimulation in the dog, on conduction at the A-V junction, during recovery from a dose of quinidine, which had sufficed to eliminate temporarily all vagus effects. In the foregoing paper this effect is discussed, and attention is drawn to its similarity, in some respects, to the reversed effect of the vagus on the cat's heart, described some years ago by Laidlaw, Symons and myself,<sup>1</sup> as a sequel to the injection of small doses of nicotine, of curari, or of certain other alkaloids having a similar type of action. My colleagues inclined to a different interpretation of their phenomenon, but suggested that I should test the possibility of producing, by means of quinidine, the type of reversal which nicotine causes in the action of the cat's vagus. I have made four such experiments on cats under paraldehyde, and have in three of them seen the reversal of the effect of the vagus on the sinus rhythm of the cat's heart, which we described previously. The reversed action is produced by quinidine neither so easily nor in such striking form as by nicotine, but the effect is unmistakably of the same kind. Like the reversed effect on conduction at the A-V junction in the dog, it is seen during recovery from a dose of quinidine sufficient to annul the effect of the vagus on the sinus rhythm of the cat's heart. The first sign of recovery is seen in a slight retardation of the rhythm for the space of a few beats at the commencement of a period of strong faradisation of the vagus. This weak inhibition is rapidly evanescent, and no further effect is seen while stimulation of the vagus is continued. The cessation of the stimulation, however, is followed by the appearance and prolonged persistence of a retardation, which is removed by renewal of vagus stimulation, and reappears when this is again interrupted: so that successive renewals and interruptions produce the appearance of inhibition *between* and acceleration *during* the periods of vagus stimulation. Fig. 1 shows the effect at this stage, as recorded by a mercurial manometer.



*Cat.* 3 kilos. Paraldehyde. 4th and 5th periods of strong stimulation of vagus, during early period of recovery from 60 mgn. of quinine bisulph.

While the production of this reversal by quinidine in the cat, which is certainly the same phenomenon as I described in conjunction with Laidlaw and Symons, strengthens the suggestion that the phenomenon described in the preceding paper is of the same type, the difficulties in the way of an identification, which are there indicated, remain untouched. There is one other point on which the evidence seems to be clearer. The partial or complete paralysis of vagal action produced by quinidine is not due to an atropine-like action. Whether the effect of the vagus is completely annulled, or exhibits the delay and paradoxical reversal above described, a peripherally acting substance such as acetyl-chlorine produces its typical vagomimetic inhibition without impairment or modification. Neither the peripheral structure which atropine paralyses, nor the response of the cardiac muscle to this type of inhibitor stimulus, seems to be affected by quinidine. So far as the facts warrant any suggestion, the similarity of its action to that of nicotine, curari, etc., would appear to indicate the autonomic cell-station on the vagus path as the level at which the paralytic effect is produced by quinidine.

It is desirable, perhaps, again to emphasise the fact that paraldehyde, in such experiments, is not merely an anæsthetic, but directly facilitates the production of the reversed vagus action. I have recently, for the first time, observed the vagus paradox, as the result of strong faradisation of the nerve, in a cat under the ordinary anæsthetic dose of paraldehyde, without the use of any other drug. Such an occurrence is rare, but it raises a strong presumption that the action of the vagus on the heart is never perfectly normal in the cat under paraldehyde.

## REFERENCE.

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## VENTRICULAR HYPERTROPHY.

### A COMPARISON OF ELECTROCARDIOGRAPHIC AND POST-MORTEM OBSERVATIONS.

By GEORGE R. HERRMANN and FRANK N. WILSON

(Ann Arbor).

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WHEN Einthoven<sup>3,4</sup> began to apply the string galvanometer to the study of heart disease he observed that certain valve lesions, when accompanied by great cardiac enlargement, yielded electrocardiograms of distinctive type. In cases of mitral disease in which preponderant hypertrophy of the right ventricle was believed to be present, the tallest *Q.R.S.*-summit occurred in lead *III* and the greatest downward deflection in lead *I*. In aortic insufficiency and in other conditions in which preponderant hypertrophy of the left ventricle appeared to be present, the electrocardiographic picture, when compared with that of mitral disease, was inverted: the tallest summit occurred in lead *I*, the deepest deflection in lead *III*. Einthoven also noted that these abnormal curves were often of great amplitude.

Einthoven did not attempt to give a complete explanation of the mechanism through which hypertrophy of the one or the other ventricle produces characteristic changes in the form of the electrocardiogram. He appears to have believed these changes due to some peculiarity of the spread of the excitation process such that in left ventricular hypertrophy, the first region activated, or the region of greatest initial activity, lay near the cardiac apex, while in right ventricular hypertrophy this region lay more toward the ventricular base. Whether he believed that unilateral hypertrophy was accompanied by modifications of the conducting system itself, or whether he believed only that it altered the positional relation of the ventricular regions which normally receive the impulse earliest to the muscle mass as a whole, is not clear.

Einthoven's observations have been confirmed repeatedly and extended. We need refer here only to the work of Lewis,<sup>9</sup> which may be briefly summarised as follows :—

(1) In aortic insufficiency, Einthoven's signs of left ventricular hypertrophy are usually, but not invariably, found. In rare instances the electrocardiogram may suggest right ventricular hypertrophy rather than left. The average values of the individual electrocardiographic deflections in a large series of cases show, as compared with the average values for normal subjects, a conspicuous increase in the amplitude of *R*1 (*R* in lead *I*) and *S*3\* and a decrease in the amplitude of *S*1 and *R*3; that is, the average curve exhibits, in some measure, the signs of preponderant hypertrophy of the left ventricle.

(2) In mitral stenosis, Einthoven's signs of right ventricular hypertrophy are the rule, and are shown, in some degree, by the average curve. Cases which fail to follow the rule, though less frequent than in aortic insufficiency, are not uncommon.

(3) In congenital heart disease the average values of the various deflections indicate a much greater degree of right ventricular preponderance than do the corresponding average values in mitral stenosis. It is in congenital pulmonary stenosis that Einthoven's signs of right ventricular hypertrophy are most fully developed.

(4) The electrocardiogram of the new-born infant shows the signs of right ventricular preponderance almost invariably. These disappear gradually, and, between the third and fourth months of life the curve approaches the form seen in the normal adult.

(5) Many normal electrocardiograms exhibit Einthoven's signs of right or of left ventricular hypertrophy in minor degree, and normal electrocardiograms may be divided into two classes according as they conform more to the former type or to the latter.

These observations tended to confirm Einthoven's contention that unilateral hypertrophy produces characteristic electrocardiographic signs. It was necessary, however, to explain the absence of these signs in many cases of aortic insufficiency and of mitral stenosis; for it was believed that

\* Einthoven called the chief initial deflection, when, in left ventricular hypertrophy, it was downward, an inverted "*R*"; Lewis calls this deflection "*S*." In this article we have adhered to the terminology of the latter. It is unquestionably true that this deflection is produced by the same muscle activity that gives rise, in the same cases, to the exaggerated *R*1; and we have, perhaps, no more right to call it "*S*" than we have to call the inverted *R*1 of dextrocardia "*S*." It is convenient, however, to avoid speaking of inverted deflections. The deflections of abnormal electrocardiograms are never to be considered identical in origin with the corresponding deflections of the normal electrocardiogram, and yet it seems unnecessary to invent a new terminology for each abnormal type of curve. It should be remembered that the exaggerated "*S*" of preponderance curves is more nearly analogous to the corresponding deflection of bundle-branch block curves than to the normal *S*.



unilateral hypertrophy was almost invariably present in these disorders: and to explain their presence in the new-born and in certain normal adults. Lewis sought the explanation of these difficulties in a study of the relative weight of the two ventricles under various circumstances. He devised a method of sectioning the heart which permits the muscle of each ventricle and that of the septum to be weighed separately. The ratio  $L/R$  may then be determined by dividing the weight of the left ventricle by that of the right, the weight of the septal muscle being neglected. When this method had been carried out in a large series of cases it was found that although preponderant hypertrophy of the left ventricle is the rule in aortic insufficiency and preponderant hypertrophy of the right, in mitral stenosis, numerous exceptions occur. The absence of the expected electrocardiographic signs in certain patients with these valve lesions thereby became intelligible. It was found also that the average value of the ratio  $L/R$  was higher in aortic insufficiency and lower in mitral stenosis than in a series of controls: this seemed to explain the form of the average curve in each type of case. The ratio  $L/R$  of the controls varied within wide limits, and the occurrence of signs of slight right or slight left preponderance in normal individuals could be attributed to unusual variations in this ratio. And, lastly, Müller in a similar study of the relative weight of the two ventricles, had found that the right ventricle of the new-born infant is considerably heavier in comparison with the left than is that of the adult, and that this condition persists until about the third month of life.

These results seemed to offer a complete explanation of the occurrence of the electrocardiographic signs in question and to place Einthoven's views upon a solid foundation. A more direct test of the value of these signs was, however, attempted. In nine cases the ratio  $L/R$  and the electrocardiographic signs of unilateral hypertrophy exhibited before death were compared. Six cases have been added to this series by Cotton<sup>2</sup>. Except in two of these fifteen cases the electrocardiographic indications and the type and degree of preponderant hypertrophy present corresponded remarkably well.

The following explanation offered by Lewis<sup>3</sup> for the occurrence of characteristic electrocardiograms in association with unilateral hypertrophy is based upon his interpretation of the normal ventricular complex. He has shown that the normal  $Q.R.S.$  group is produced by the algebraic summation of the left ventricular electrocardiogram (levocardiogram) and the right ventricular electrocardiogram (dextrocardiogram).<sup>\*</sup> The early phases of these curves have been recorded, and the part that each plays in the formation of the normal  $Q.R.S.$  group has been established:  $Q_1$  and  $S_3$  are left ventricular effects:  $Q_3$  and  $S_1$  are right ventricular effects:  $R_1$

<sup>\*</sup> As Einthoven<sup>4</sup> has pointed out, the statement that the ventricular electrocardiogram is the result of summation of right and left ventricular effects is equivalent to the assertion that the whole is equal to the sum of its parts. But the right and left ventricles, as opposed to the base and apex, for example, are natural subdivisions; each ventricle has its own conducting system, and is, therefore, in some measure, capable of independent activity.

is chiefly a left, and *R3* chiefly a right ventricular effect. Lewis concluded, therefore, that the tall *R1* and deep *S3* of left ventricular hypertrophy are the result of preponderance of the levocardiogram, while the tall *R3* and deep *S1* of right ventricular hypertrophy are the expression of preponderance of the dextrocardiogram. He pointed out that, in accordance with this view, *Q1* is large in left and *Q3* in right ventricular preponderance. His demonstration that anti-clockwise rotation of the electrical axis is common to both the levocardiogram and the curves of left ventricular preponderance, while the dextrocardiogram and right ventricular preponderance curves show clockwise rotation, also supports this conclusion.

The problem of explaining Einthoven's signs was thus reduced to the problem of explaining how preponderant hypertrophy of the one or the other ventricle gives rise to preponderance of the corresponding unilateral electrocardiogram. In the normal electrocardiogram the effects of the two ventricles are fairly well balanced, in spite of the greater mass of the left: nevertheless, it seems not improbable that the amplitude of the electrical effects of either ventricle depends, in some measure at least, upon its mass. A relative increase in the mass of the one or the other chamber may destroy the balance between right and left ventricular effects and enable the corresponding unilateral electrocardiogram to dominate the combined curve.

### *Methods.*

In collecting the material upon which this article is based, we had in mind the addition of a considerable number of cases to the series already reported<sup>2,9</sup>. This seemed desirable in order that the relation between the ratio *L R* and Einthoven's signs might be more exactly determined. We have followed, for the most part, the methods used by the authors mentioned, so that our data might be comparable to theirs. In order, however, to obtain as many cases as possible we have not restricted our attention to examples of cardiac disease. In Barnes Hospital, where the work was done, electrocardiograms were made routinely in all instances in which cardiac abnormalities were known to be present or were suspected to exist. For the purposes of this study, electrocardiographic observations were also made upon all patients who were critically ill, whatever the primary disease might be. As a result, our series of cases differs from those of Lewis and Cotton in that it includes many cases in which hypertrophy of the heart was not present.

The *electrocardiograms* were made by one of the authors or by Miss Lillian Pinkert, technician of the Washington University Heart-Station. The curves were standardized in the usual way and the effect of introducing a difference of potential of one millivolt into the circuit containing the string, and the patient was photographed in each instance. In measuring

the curves corrections were made for errors in standardization. When conspicuous overshooting was present, due to high skin resistance, the curves were discarded. In most of our cases only one series of curves was taken. In those instances, in which curves were made on several occasions, only the final curves were measured, except in a few cases in which they differed conspicuously in form from the curves made previously.

*Method of preparing and sectioning the heart.* In order to allow a more complete examination of the heart at the time of the post-mortem it was necessary to make some minor alterations in the method of preparing the heart for sectioning which Lewis employed.

One of the authors attended the autopsy and received the heart freed of the parietal pericardium and with the large vessels cut short. The organ being weighed, the auricles were removed, and the mitral, aortic, tricuspid and pulmonary valves were carefully examined and tested by the hydrostatic test. The mitral and tricuspid leaflets were then removed and the aorta and pulmonary artery were separated from the ventricular muscle. The valve leaflets, vessels, and auricular muscle were then returned to the pathologist for further examination.

The capacity of each ventricle was determined\* by measuring the volume of mercury necessary to fill its cavity. Long pins were thrust through the ventricular base and, with the mercury still in place, the heart was suspended in a vessel containing 10 per cent. formol. From this point onward the method of Lewis was strictly followed up to the time when the organ was sectioned.

Unfortunately, Lewis has described his method of sectioning the heart but briefly, and we misunderstood his directions. The first cut was made parallel to and along the right margin of the septum in such a way that the cavity of the right ventricle remained closed on its septal side by a very thin slice of septal tissue. The cut was begun posteriorly and was brought forward until it reached the conus tendon, which was then followed as in the method of Lewis. On the anterior surface of the heart the cut followed the interventricular sulcus. This cut was continued downward until the right ventricle was completely separated from the remainder of the heart muscle. The second cut was made tangential to the cavity of the left ventricle on its septal side, but instead of being carried straight through to the centre of the conus tendon, its anterior part was curved to the left so that it was maintained parallel to the first cut throughout its course.†

We did not discover our error until the first fifty hearts of our series had been divided: these hearts were afterwards resectioned according to the method of Lewis, which was followed in the remaining cases. We felt,

\* The ventricular capacities of the first twenty hearts obtained were not measured. These hearts were maintained in a distended condition by filling the ventricular cavities with cotton wool.

† This method is referred to hereafter as method A.

especially with the first method employed, some uncertainty in making the cuts, and sought some way in which this might be avoided. The following method of separating the right and left ventricles seems to us less arbitrary and less subject to error than those heretofore employed. The fixed ventricles are divided by cuts at right angles to the long axis of the heart into a series of sections, each about  $1\frac{1}{2}$  cm. in thickness. If this is done with a sharp knife, a thin but clear-cut line, formed by the scroll muscle layers, will be seen running through the centre of the septum in an anterior-posterior direction. This line is well shown in Fig. 9, a photograph of one of the sections of the heart in Case 25. Each section is divided into right and left divisions by a cut which follows this line throughout its course; near the anterior and posterior surfaces of the heart where the line forks, the cut bisects the angle between the forks. The septal muscle is distributed by the cut between the two ventricles and is not considered separately. This method (method B) was employed in 29 cases: the heart was resectioned in all instances by our first method (method A) followed by that of Lewis or by the latter method alone. The muscle weights obtained by method B are given in Table III; the muscle weights obtained on resectioning are included so that the various methods used may be compared.

It will be seen that the ratio  $L/R$  determined by method B is invariably lower than that determined by the method of Lewis and also lower than that determined by method A. The average difference between the ratio  $L/R$  determined by the Lewis method and the ratio  $L/R$  determined by method B is 0.23; the maximal difference is 0.68 and the minimal difference 0.04. When the ratio  $L/R$  is high the difference appears to be greater than when it is low: thus for ten cases with  $L/R$  ratios ranging from 3.59 to 1.96 (Lewis method) the average difference is 0.35; for 10 cases with ratios ranging from 1.94 to 1.69, it is 0.22; and for 9 cases with ratios ranging from 1.61 to 1.12, it is 0.13. Assuming that the methods may be carried out with equal accuracy, the maximal error in the ratio  $L/R$  determined by either method will amount to approximately one-half the difference between the maximal (or minimal) and the average difference for a small range of  $L/R$  values. For our first group of cases (ratios between 3.59 and 1.96) the maximal difference is 0.68 and the average difference 0.35; the maximal error is, therefore, about 0.13. It appears from the table, however, that errors as great as this seldom occur.

It will be noted that when the hearts were sectioned by the Lewis method the average ventricular weight was about 18 grams less than when the first cuts were made. The hearts had been stored in weak formol for some time, and although they were again placed in water for several days, they did not regain their original weights.

When the last cuts were made, the thickness of the lateral wall of each ventricle at the junction of its basal and middle thirds was measured.

*Description of observations.*

*Tables I, II and IV.* Our observations are summarised in tabular form: the details of the clinical and post-mortem observations are given in Table I. The cases are arranged in the order determined by the ratio *L R* (Lewis method), beginning with the highest ratio and ending with the lowest. The term "heart weight" refers to the weight of the fresh heart as it was received from the pathologist. The figures for height and weight and the notes upon the condition of the kidneys and heart valves were abstracted from the pathological records: the blood pressure readings, from the clinical records. The last column of the table contains additional notes relative to the condition of the cardiovascular system and to other matters of interest.

The electrocardiographic measurements are given in Table II: the age, ventricular weight, and ratio *L R* are repeated here for comparison. The final column of the table gives the most important or the primary disease. Electrocardiographic measurements which fall outside the normal limits determined by Lewis and Gilder<sup>10</sup> are printed in italics. The index was computed by subtracting the sum of *R3* and *S1* from the sum of *R1* and *S3*. The normal range of the index is not given by Lewis and Gilder, but was determined from their tables: the maximal index in their series of 52 cases is 8.5: the minimal index is -14. Indices which fall outside these limits are printed in italics. Certain positive indices are followed by one or by two stars to indicate that the corresponding electrocardiograms show one (one star) or both (two stars) of the following signs of left ventricular preponderance: (*a*) the tallest summit occurs in lead *I*, (*b*) the deepest deflection occurs in lead *III* and exceeds the normal limit of 0.45 millivolt.\* Stars follow negative indices when the corresponding signs of right ventricular preponderance are present: the normal limit for *S1* is 0.60 millivolt.

In Table IV the average values of the electrocardiographic measurements and muscle weight determinations in various types of cases are given. Lewis's average values for controls, for aortic insufficiency, and for mitral stenosis are included for comparison.

*The normal range of the ratio L R and of the ventricular weight body-weight ratio.* In Lewis's series of "cancer controls" the ratio *L R* ranges from 1.46 to 2.06: in his series of "controls," from 1.57 to 2.18: in Cotton's series of controls, from 1.43 to 2.28, providing Case 10, an infant aged 2 days, be excluded. In our own series of controls (Table IV) it ranges from 1.46

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\* It is probable that this limit is too low. We have seen a number of electrocardiograms of apparently normal individuals in which *S3* reached a value of 0.60 to 0.70 millivolt. We have adopted throughout the normal limits determined by Lewis and Gilder. The number of subjects studied by them was not large, but they were selected with great care. For the purposes of this article the exact limits of normality are not of great importance.

to 2.14: or, if those cases in which an abnormal electrocardiogram was the chief cardio-vascular abnormality be excluded, from 1.46 to 1.96. Müller,<sup>12</sup> who used a different method of sectioning the heart, considers 0.400 the lower, and 0.650 the upper normal limit for the ratio  $R/L$ : these figures correspond to  $L/R$  ratios of 2.50 and 1.54 respectively. In all series of controls in which the Lewis method was used the average value of the ratio  $L/R$  lies in the immediate neighbourhood of 1.80. For the purposes of this study, we consider ratios above 2.20 or below 1.50 abnormal.

In Table I we give for each case the ratio of the ventricular weight in grams to the body weight in grams. This ratio was computed also in all of the control cases published by Lewis. In his series of "cancer controls" it varies between 0.00200 and 0.00421 (average value 0.00301): in his series of "controls" it ranges from 0.00276 to 0.00480 (average value 0.00386). In our own series of controls it ranges from 0.00170 to 0.00390 (average value 0.00292). Müller's average values for this ratio range from 0.00371 to 0.00489. We believe that ratios above 0.00500 indicate definite ventricular hypertrophy.

*Comparison of the ratio  $L/R$  and the electrocardiographic signs of preponderance of the one or the other ventricle.*

Examination of Table II indicates that the relation between the form of the  $Q.R.S.$  group and the relative weight of the two ventricles is much less close than is, at present, generally believed. In order to get a more exact idea of this relation in our series of cases we have divided them, on the basis of the ratio  $L/R$ , into four groups:—

*Group I.— $L/R$  ratio above 2.20; abnormal left ventricular preponderance.* Fifteen of our cases fall in this group. In only two of these does the final electrocardiogram indicate definite left ventricular preponderance (index positive, two stars). In four instances it indicates questionable left ventricular preponderance (index positive, one star). In four instances the final curve shows a tendency toward left ventricular preponderance (index positive, no star), and in five instances, a tendency toward right ventricular preponderance (negative index, no star). If we consider all the curves made, instead of the final curves alone, an abnormal degree of left ventricular preponderance might, perhaps, be suspected from the form of the electrocardiogram in eight cases. It is noteworthy that in five of these eight cases the ventricular weight exceeds 300 grams. Of the remaining seven cases in which the electrocardiogram shows no evidence of abnormal left ventricular preponderance the ventricular weight exceeds 300 grams in none; in only one does it exceed 200 grams.

*Group II.*—*L R ratio 1.80 to 2.20, both inclusive, left ventricular preponderance within normal limits.* Sixteen of our cases fall in this group. The electrocardiogram indicates definite left ventricular preponderance in four cases, and questionable left ventricular preponderance in one. In three of these five cases the ventricular weight exceeds 250 grams. In nine cases the electrocardiogram indicates a tendency toward left ventricular preponderance; in one instance the index is zero. In one instance the electrocardiogram indicates questionable right ventricular preponderance. In none of these eleven cases does the ventricular weight reach 200 grams.

*Group III.*—*L R ratio 1.50 to 1.78 (inclusive), right ventricular preponderance within normal limits.* Twenty-one of our cases fall in this group. In one case the electrocardiogram indicates definite left ventricular preponderance; in one case it indicates definite right ventricular preponderance. In both of these cases the ventricular weight is low. In seven cases the electrocardiogram indicates a tendency toward left ventricular preponderance, and in eleven cases a tendency toward right ventricular preponderance; in one case the index is zero. In none of these nineteen cases does the ventricular weight reach 250 grams.

*Group IV.*—*L R ratio below 1.50, abnormal right ventricular preponderance.* In this group there are but seven cases; in none of these does the electrocardiogram indicate either definite or questionable right ventricular preponderance. In three cases it indicates a tendency toward right ventricular preponderance, and in an equal number of cases, a tendency toward left ventricular preponderance. In only one of these six cases does the ventricular weight exceed 250 grams. In one case the electrocardiogram indicates definite left ventricular preponderance; in this instance the ventricular weight is 199 grams. To sum up in tabular form:—

Group.	No. of cases.	Definite left prepond.	Quest. left prepond.	Tend. to left prepond.	Tend. to right prepond.	Quest. right prepond.	Definite right prepond.
I.	15 (5)*	2 (2)	6 (3)†	3 (0)	4 (0)	0 (0)	0 (0)
II.	16 (3)	4 (2)	1 (1)	9 (0)	0 (0)	1 (0)	0 (0)
III.	21 (0)	1 (0)	0 (0)	7 (0)	11 (0)	0 (0)	1 (0)
IV.	7 (1)	1 (0)	0 (0)	3 (0)	3 (1)	0 (0)	0 (0)

\* The numbers in parentheses indicate the number of cases in which the ventricular weight exceeds 250 grams.

† If all the curves taken, and not the final curves alone, be considered.



There appears to be a distinct relation between the ventricular weight and the frequency with which the electrocardiographic signs of preponderance occur. Of our 59 cases, 22 show  $L/R$  ratios outside the normal range. The signs of definite or questionable preponderance are found 5 times in 6 instances in which the ventricular weight exceeds 250 grams: they are found but 4 times in the 16 instances in which it falls below this figure. The signs of preponderance are, furthermore, much more reliable when the heart is greatly hypertrophied than when it is of relatively normal weight. The ratio  $L/R$  is above the normal average in every instance in which the signs of left ventricular preponderance are associated with a ventricular weight of over 250 grams: it is below the normal average in 2 of 7 cases in which these signs are associated with a ventricular weight of less than 250 grams. When the heart is of normal weight or is only slightly hypertrophied, there appears to be very little relation between the form of the electrocardiogram and the ratio  $L/R$ . The close relation which is found in the series of Lewis and Cotton is undoubtedly due to the fact that they dealt exclusively with greatly hypertrophied hearts: in only one of the fifteen cases published by them does the ventricular weight fall below 250 grams.

The relation between the ventricular weight and the occurrence of preponderance curves is well shown by the average values of Table IV. In all of those instances in which the average index indicates a conspicuous degree of right or left preponderance, in aortic insufficiency, in mitral stenosis, and in chronic hypertension, the average ventricular weight is high (250 grams or over), whereas in other groups of cases, in which the average  $L/R$  ratio is equally abnormal but in which the average ventricular weight is low, the signs of preponderance are present in a much less evident degree.

*The failure of a definite relation between the form of the electrocardiogram and the ratio  $L/R$  when the heart is of relatively normal weight.*

Does the failure of a definite relation between the form of the electrocardiogram and the ratio  $L/R$  when the ventricular weight falls below 250 grams mean that we must abandon our present conception of the manner in which preponderance curves arise, and must we attribute the apparent relation when the heart is greatly hypertrophied to as yet unknown causes? Or does it mean that the ratio  $L/R$  is but one of several factors determining the form of the ventricular complex and that its influence increases as the ventricles increase in weight? In attempting to answer these questions it is necessary to consider the origin of preponderance curves from the theoretical standpoint and to examine certain factors which may disturb the relation between the  $L/R$  ratio and the form of the electrocardiogram.



*Relation of the mass of the heart to the amplitude of its electrical effects.*  
Our present conception of the origin of preponderance curves is based upon the fundamental assumption that there is a relation between the mass of the heart muscle and the magnitude of the potential difference which it produces. Does such a relation exist?

This question is a difficult one to answer: for the "manifest" potential difference at the body surface is a function of many variables. It is true that the electrocardiogram of an infant does not differ materially in amplitude from that of an adult, although the heart of the latter is many times the more massive. But this may be due to the fact that the "manifest" potential difference decreases as the distance of the electrodes from the heart increases. We know also that the "manifest" potential difference must vary with the conductivity of the tissues that surround the heart and with the plane of the electrodes, and that variations in the amplitude of the electrical deflections may occur with variations in the contractility of the heart muscle.<sup>6</sup> These and other similar factors tend to obscure any possible relation that may exist between the amplitude of the electrocardiogram and the weight of the heart. Since, however, most of them must affect the "manifest" potential differences produced by the two ventricles in approximately the same way and to the same degree,\* they will not disturb a possible relation between the relative mass of these two chambers and the relative amplitude of their respective electrical effects.

Although the left ventricle is normally 1.8 times as heavy as the right, the two chambers produce electrical effects of approximately equal amplitude. If we hold that there is a relation between the mass of each ventricle and the amplitude of the corresponding unilateral electrocardiogram, we must admit that each gram of right ventricular muscle is equivalent, so far as its electrical efforts are concerned, to 1.8 grams of left ventricular muscle. Such a relation is by no means as impossible as it sounds. The levocardiogram and the dextrocardiogram are resultants: each is produced by a combination of opposed forces, and its amplitude is, therefore, a measure of the degree in which one group of forces overbalances the other. The distribution of the ventricular muscle may be such as to cause a greater lack of balance between the opposed forces of the right ventricle than between those of the left. It is possible also that the right ventricle is more advantageously placed than the left in that its major electrical axis (the electrical axis at the time when the difference of potential is at its

\* The influence of the conductivity of the tissues which surround the heart upon the form and amplitude of the electrocardiogram is difficult to estimate. If all tissues of the body conduct electrical currents equally well, then the "manifest" potential difference between two points at the body surface should vary inversely with the conductivity of the tissues. If, on the other hand, the conductivity of the heart muscle differs from that of the surrounding tissues, then the proportion of the total current that flows in the heart itself will vary with the relative conductivity of the cardiac tissue and the adjacent tissue. The left ventricle is surrounded by air containing lung while the right ventricle lies adjacent to the liver and the anterior chest wall; it is possible that this may affect the relative amplitude of the effects of these chambers at the body surface.

maximum) falls more nearly in the plane of the three leads. And lastly, the thinness of the wall of the right ventricle compared to that of the left and possibly the arrangement of its conducting system may cause a greater concentration of its electrical efforts in that, during a part of the *Q.R.S.* interval, a greater percentage of the right than of the left ventricular muscle is simultaneously passing into the active state. Finally, it should be pointed out that in the bird, in which the left ventricle is more than three times as heavy as the right, the levo-cardiogram dominates the bigram completely.

So far as we can see, then, there are no facts seriously in conflict with the belief that that there is a relation between the mass of the one or the other ventricle and the amplitude of the corresponding unilateral electrocardiogram. There are, on the other hand, certain facts which suggest that such a relation does exist. The association of preponderance curves with aortic insufficiency, mitral stenosis, pulmonary stenosis, and chronic hypertension and their occurrence in the new-born is, at present, difficult to explain on any other basis. Of equal importance is the fact that electrocardiograms of enormous amplitude often accompany great cardiac hypertrophy. The maximal deflection of the normal electrocardiogram seldom exceeds a value of 2 millivolts, whereas in pulmonary stenosis deflections exceeding 4 millivolts are not infrequently encountered (Fig. 5). Deflections of this amplitude never occur, so far as we know, in the absence of great hypertrophy of the heart.

To sum up, we may say that the present-day theory of preponderance curves gives a more simple and rational explanation of the known facts than any other that has been proposed, and that there are no facts seriously\* in conflict with it.

*The influence of the relative weight of the two ventricles and of their absolute weight upon the form of the electrocardiogram; from a theoretical standpoint.* Typical preponderance curves bear a striking resemblance to the curves of

\* Certain minor conflicts should be noted. It has been pointed out that in left ventricular preponderance *Q* is usually most prominent in lead *I*, whereas in right ventricular preponderance *Q* is usually most prominent in lead *III*. This deflection is thought to be produced by the activation of the upper septum, and since, when the two ventricles receive the impulse simultaneously, the excitation wave spreading from the right conducting system and that spreading from the left conducting system should meet at the centre, approximately, of the upper septum, regardless of the type or degree of hypertrophy present, it is difficult to see why the form of *Q* should depend upon the relative weight of the two ventricles. Our ideas concerning the origin of *Q* may, however, be erroneous.

It is also true that in certain cases of left ventricular preponderance there is a definite *S* deflection in lead *I* and a corresponding final upward deflection in lead *III*. According to our present ideas, these deflections must be right ventricular effects. How is it possible for a right ventricular effect to show itself at the end of the *Q.R.S.* interval when there is great preponderant hypertrophy of the left ventricle? If the two ventricles receive the impulse simultaneously, the spread of the excitation wave should be complete on the right side before it is complete on the left, and even if it is not, the left ventricular effects should predominate.

And, lastly, if preponderant hypertrophy of the one or the other ventricle produces characteristic modifications of *Q.R.S.*, why does it not produce characteristic modifications of *T*? It is possible, of course, that, since *T* is much more readily modified by various factors than is *Q.R.S.*, its variability of form in preponderant hypertrophy may be the result of the myocardial changes that accompany most forms of heart disease.

bundle branch block: in the one instance the effects of one ventricle overbalance the effects of the other; in the other instance the effects of one ventricle precede the effects of the other. When these curves are analysed it appears that their peculiarities of form are due chiefly to the abnormal position of the major electrical axis. Now the position of the major electrical axis is dependent (see Fig. 1) upon the relative magnitude and not upon the difference in magnitude, of the potential differences produced by the two

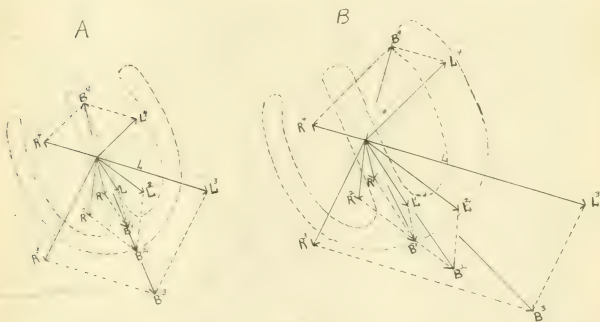


FIG. 1.

- A. A diagram illustrating the manner in which right and left ventricular effects combine when the heart is normal.  $R$ .—Electrical axis of the right ventricle.  $L$ .—Electrical axis of the left ventricle.  $B$ .—Resultant electrical axis.
- B. A similar diagram illustrating the manner in which right and left ventricular effects combine when the left ventricle is greatly hypertrophied.

ventricles. Other factors being the same, the form of the electrocardiogram (*i.e.*, the position of the major electrical axis) should vary with the  $L/R$  ratio; the amplitude of the electrocardiogram should vary with the weight of the ventricular muscle. Why, then, do we find that large hearts are more prone to yield preponderance curves than are small hearts with equally abnormal  $L/R$  ratios? In the first place it is probable that other factors, such as the arrangement of the ventricular conducting system, which influence the form of the electrocardiogram, disturb the effect of the ratio  $L/R$  less when the heart is greatly hypertrophied than when it is of relatively normal size. In the second place, although the normal right ventricle produces effects of greater amplitude, in proportion to its mass, than the left, it does so, according to our theory, because of certain factors previously mentioned which can hardly escape modification when the heart hypertrophies.

*Comparison of the  $L-1.8 R$  value and the electrocardiogram.*

Since it is usual, in judging the degree of preponderance shown by the electrocardiogram, to consider the amplitude as well as the direction of the chief deflections, and since preponderance curves are more prone to occur with large than with small hearts, it seems logical, when comparing electrocardiographic and post-mortem observations, to substitute for the ratio  $L/R$  some figure which is in part dependent upon the ventricular weight. Such a figure may be obtained by subtracting, from the weight of the left ventricle, 1.8 times the weight of the right.

In Table V we have arranged our cases in the order determined by the  $L-1.8 R$  value, and in Table VI we have arranged in the same way the nine cases published by Lewis, the six cases published by Cotton, and all of our own cases in which the ventricular weight exceeds 250 grams. These tables indicate that, on the whole, there is a closer relation between the form of the electrocardiogram and the  $L-1.8 R$  value than between the form of the electrocardiogram and the ratio  $L/R$ . We find, for instance, definite or questionable preponderance in all but one of the seven cases (Table VI) in which the  $L-1.8 R$  value is greater than 70 or less than  $-70$ , and the discordances which occur in cases with abnormal  $L/R$  ratios but relative normal ventricular weights (Table V) are rendered much less conspicuous. Nevertheless, the  $L-1.8 R$  value and the form of the electrocardiogram fail to correspond in many instances, and occasionally notable discrepancies between them are encountered. Some of these are due, perhaps, to the failure of the normal 1.18 ratio to hold when the heart hypertrophies; others are probably due to factors still to be considered.

*Errors in determining the ratio  $L/R$ .* In a previous section of this article we have estimated the maximal error in the ratio  $L/R$  due to inaccuracy in sectioning the heart to be about 0.13. A case which falls near the upper limit of a group (page 99) may, had the cuts been made without error, have fallen in the next higher group; a case which falls near the lower limit of a group may have fallen in the next lower group. It is clear, therefore, that, even if we assumed that the maximal error occurred in every case, our chief conclusions as to the relation between the form of the electrocardiogram and the ratio  $L/R$  would not be greatly altered. But as shown by Table III, and by a comparison of our normal averages with those of Lewis (Table IV), the error in determining the  $L/R$  ratio is usually very small.

*Changes in the ratio  $L/R$  between the last electrocardiographic examination and death.* It has been shown by Stewart<sup>14</sup> that when aortic insufficiency is produced in dogs the heart may be definitely hypertrophied at the end of the first week; comparatively little hypertrophy takes place after the fourth week. Unless, therefore, the final electrocardiogram is taken within a few days of death, a change in the ratio  $L/R$  may take place after it is made.

In the majority of our cases only a few days elapsed between the last electrocardiographic examination and death: furthermore, the disease process present was in most instances of long standing, so that it is improbable that hypertrophy of the heart was taking place rapidly when our observations were made. In those cases in which the patient was under observation for a long time, and in which a series of curves was made, all of the curves were usually almost identical in form, and in no instance did they indicate a progressive increase or decrease in right or left ventricular preponderance.

*Variations in the position of the heart.* It has been held by some that those abnormalities of the electrocardiogram, which are now believed to be due to preponderant hypertrophy of the one or the other ventricle, might arise through abnormal variations in the position of the heart. That somewhat similar curves may be produced by rotation of the heart about its anterior-posterior axis may be demonstrated in a very simple way. To determine the effect of counterclockwise rotation of 60 degrees it is necessary only to substitute lead *II* for lead *I*, lead *III* for lead *II*, and lead *I*, inverted, for lead *III*; the inverted lead must be read from right to left. By repeating this process the effect of rotating the heart 120, 180, or 240 degrees may be seen. By reversing the process the effect of clockwise rotation may be estimated. If these procedures are carried out upon a normal electrocardiogram, it will be seen that counterclockwise rotation of the heart gives a picture resembling that of left, and clockwise rotation, a picture resembling that of right ventricular preponderance. It will be evident, however, that rotation of the heart produces abnormalities of *P* and *T* which do not occur in preponderance curves, and that, furthermore, in order to produce curves which resemble many of the curves obtained from patients with preponderant hypertrophy of one ventricle, a much greater rotation of the heart is necessary than could possibly take place in the body. This has already been pointed out by other writers.\* It is clear, then, that rotation of the heart about an anterior-posterior axis cannot account for preponderance curves of typical form. It is also known that displacement of the heart without rotation, such as is brought about by pleural effusion, or pneumothorax, has but little effect upon the form of the electrocardiogram. Regarding the effects of rotation of the heart about its long axis or about a vertical axis, we know very little.\*

That the form of the normal electrocardiogram is to a considerable degree dependent upon the position of the heart is well known. It is a matter of common observation that short, stout individuals (hypersthenic habitus) with transversely placed hearts usually yield electrocardiograms in which lead *III* is the lead of least amplitude, not only with respect to *Q, R, S*, but also with respect to *P* and *T*. It is in this type of individual that *Q, R, S*,

\* Boden and Neukirch (*Pflüger's Archiv.*, 1918, clxxi, 146) believe that preponderance curves may be produced by rotation of the heart about its long axis. Their experiments upon the isolated human and animal heart are not, it seems to us, convincing.

of lead *III* is often of bizarre form: the inversion of *T3* in association with these peculiar *Q.R.S.* complexes, may be attributed to the transverse position of the heart. Individuals of slender build with vertically placed hearts (asthenic habitus) usually yield electrocardiograms of the opposite type in which lead *I* is the lead of least amplitude. In both types of individuals notable exceptions occur.

The effects of abnormal variations in the position of the normal heart upon the form of the electrocardiogram may be estimated by studying the effects of deep inspiration and forced expiration. Thirty experiments of this type were carried out by one of us on a series of healthy male subjects. To give some idea of the range of the effects observed, the results of five of these experiments are given in Table VII. From these figures it is clear that positive indices may become negative as the result of deep inspiration and that negative indices may become positive as the result of forced expiration. Normal curves in which lead *III* is the lead of least amplitude are almost always converted by deep inspiration into curves in which lead *I* is the lead of least amplitude. Sometimes, though less often, curves of the latter type are converted into curves of the former type by forced expiration. In our experience, normal curves have never been converted by respiratory experiments into curves in which lead *II* was the lead of least amplitude. In some instances normal curves are converted by forced expiration into curves which suggest questionable or slight left ventricular preponderance (Cases 551 and 527, Table VII). Deep inspiration, on the other hand, almost never converts a curve of the normal type into a curve suggestive of right ventricular preponderance: this is because inspiration almost invariably reduces the amplitude of all the deflections of lead *I*, even when this effect would not be anticipated. Thus in Case 630 (Table VII) *S1* is smaller in inspiration and larger in expiration, although the principles of the equilateral triangle would lead us to expect the opposite in each instance. This is probably because the respiratory changes in the position of the heart consist in rotation about its long axis as well as about an anterior-posterior axis.

Of the effect of respiratory changes in the position of the heart upon the form of the abnormal electrocardiogram we have made no systematic study: the opinions expressed below are based on many isolated observations, but further experience may require us to revise them. Typical right preponderance curves are seldom very much altered by respiratory experiments: contrary to what might be expected, inspiration often renders the signs of right preponderance less, rather than more, conspicuous. Left ventricular preponderance curves, on the other hand, are often changed profoundly. Curves in which lead *I* is the lead of least amplitude (with reference to *Q.R.S.*) are frequently converted into curves of the normal type by deep inspiration. Curves in which lead *II* is the lead of least amplitude are often converted into curves in which lead *III* is the lead of least amplitude but rarely into curves of the normal type (*i.e.*, curves in which *R* is tallest in lead *II*). Some of the more conspicuous changes in the form of the abnormal



electrocardiogram, produced by forced respiration, that we have encountered are shown in Figs. 2, 3 and 4. In Fig. 2 are shown curves indicative of questionable left ventricular preponderance which were converted by deep inspiration into curves indicating a tendency toward right ventricular preponderance. In Fig. 3 curves indicative of definite left ventricular preponderance are converted by deep inspiration into curves of the normal type. Another striking example of a similar phenomenon is shown in Fig. 4: in this instance the direction of *Q.R.S.* of a curve indicating definite left ventricular preponderance (index 36) was reversed by deep inspiration. It is evident, then, that curves indicative of definite left ventricular preponderance, more especially those in which the major electrical axis is nearly horizontal, may be converted into curves of the normal type by a change in the position of the heart such as takes place when a deep breath is taken.

*To sum up* :—Variations in the position of the normal heart account for many, though not all, of the usual variations in the form of the normal electrocardiogram from one individual to another.

Abnormal or unusual variations in the position of the normal heart may give rise to curves indicative of questionable left ventricular preponderance; these curves are usually within or just without the normal range and are of the type in which lead *III* is the lead of least amplitude. Variations in the position of the normal heart seldom give rise to curves indicative of right ventricular preponderance.

The signs of left ventricular preponderance may be absent, in cases in which they would ordinarily be present, when the heart is unusually pendulous. These signs may be exaggerated when the heart is transversely placed. The signs of right ventricular preponderance appear to be less often disturbed by such changes in the position of the heart as are dependent upon changes in the level of the diaphragm than are the signs of left preponderance.

*Differences between the effects of preponderance of the levocardiogram or dextrocardiogram and the effects of rotation of the heart.* The effects of rotation of the heart may often be distinguished from those of preponderance of the levocardiogram or dextrocardiogram; the former differ from the latter in several respects.

(1) As has already been noted, rotation of the heart produces changes in *P* and *T* similar to those which it produces in *Q.R.S.*; preponderance of the levocardiogram or dextrocardiogram does not affect *P*; its effect upon *T* is uncertain, but in any case it does not affect *T* in the same way as does rotation of the heart. In the application of this knowledge, however, considerable difficulty arises. Hearts which yield preponderance curves are prone to show other electrocardiographic abnormalities due to myocardial changes in both the auricular and ventricular muscle. Patients with heart disease often receive digitalis which produces deformities of *T*. Very large

hearts are usually transversely placed so that a combination of the effects of rotation and preponderance is obtained. Little dependence can be placed upon the form of  $P$  and  $T$ , therefore, when the heart is abnormal, in judging the position of the heart and its effects upon the electrocardiogram.

(2) It has also been pointed out that preponderance of the levocardio-gram or dextrocardiogram may produce changes in  $Q.R.S.$  which could not be simulated by such an amount of rotation of the heart as is possible in the body.

(3) Unlike ventricular preponderance, displacement of the heart can not increase the magnitude of the greatest manifest potential difference produced by the heart. Since the maximal deflection represents not less than 85 per cent. (the cosine of 30 degrees) of the greatest manifest potential difference, rotation of the heart cannot materially increase the amplitude of the tallest deflection of the three leads.\*

(4) It has been shown<sup>8</sup> that preponderance curves show on analysis a fairly uniform rotation of the electrical axis: when the dextrocardiogram preponderates, the rotation is clockwise; when the levocardio-gram preponderates, it is counterclockwise. Normal curves show some movement of the electrical axis but, usually, of a much less uniform kind. The cause of this difference between normal curves and preponderance curves is shown in Fig. 1. Fig. 1A illustrates the normal conditions. It is assumed in this figure that the electrical axis of the right ventricle shows a uniform clockwise rotation and that the manifest potential difference gradually increases until late in the  $Q.R.S.$  interval, when it rapidly decreases. Similar assumptions are made for the left ventricle, except that the rotation is counterclockwise. It is further assumed that the manifest potential difference produced by one ventricle is exactly equal, at all times, to the manifest potential difference produced by the other ventricle at the same instant. These assumptions correspond fairly well with previous observation.<sup>8</sup> When each vector that represents a right ventricular effect is combined with the corresponding left ventricular vector according to the law that governs the addition of directed quantities (parallelogram of forces), all of the resultants ( $B^1$ ,  $B^2$  and  $B^3$ ) have the same direction until late in the  $Q.R.S.$  interval, when there is a sudden reversal of direction ( $B^4$ ). The counter-clockwise rotation of the electrical axis of the left ventricle neutralises the clockwise rotation of the electrical axis of the right, so that the resultant electrical axis remains stationary, or nearly so, until late in the  $Q.R.S.$  interval, when it suddenly rotates through 180 degrees. This lack of rotation of the electrical axis

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\* This statement applies only to rotation of the heart about an anterior-posterior axis. It has been said that the potential differences developed in the anterior-posterior plane are much greater than those developed in the frontal plane (plane of the three leads). This opinion is undoubtedly based upon electrocardiograms taken by anterior-posterior leads in which the electrodes are placed close to the heart; in our experience the manifest potential differences in the frontal plane are equally large when the electrodes are similarly placed.



during the time when the manifest potential difference is near its maximum is well shown by the analyses of two normal electrocardiograms given by Lewis (Tables IX and X, Lewis,<sup>8</sup> Part IV).

Fig. 1B illustrates the conditions when the levocardiogram preponderates. In this figure the same assumptions are made as for Fig. 1A, except that it is now assumed that the manifest potential difference produced by the left ventricle is always exactly twice as great as that produced by the right ventricle at the same instant. As a result, each succeeding resultant is swung more and more to the left, and the counterclockwise rotation of the levocardiogram is impressed upon the bigram. Furthermore, the manifest potential difference tends to reach its maximum later in the *Q.R.S.* interval than is the case normally, and the vector which represents it points more to the left.

In so far as ventricular preponderance produces characteristic rotation of the electrical axis, its effects may be distinguished from those of rotation of the heart about an anterior-posterior axis, which does not affect the movements of the electrical axis, by analysis. For ordinary use this is a laborious and impractical method. Curves which show rotation of the electrical axis, during the period when the manifest potential difference is near its maximum, may, however, often be distinguished from those that do not by inspection. Certain simple tests may also be applied. It will be seen from Fig. 1A that failure of the electrical axis to rotate during the inscription of *R* will cause the chief deflections of the three leads to be in phase; they will therefore obey the rule that

Lead *I* plus lead *III* equals lead *II*.\*

In preponderance curves, on the other hand, corresponding peaks are seldom in phase: if the rotation of the electrical axis is clockwise the greatest deflection of lead *III* precedes that of lead *I*; if the rotation is counterclockwise this order is reversed.

Curves that show uniform rotation of the electrical axis do not, as a rule, show notching of the *Q.R.S.* of least amplitude: such notches are due to irregularities in the movement of the electrical axis, and especially to changes in the direction of its rotation.<sup>16</sup> For obvious reasons these are prone to occur in curves of the normal type. When not present, in the original curves, notches may sometimes be brought out by a respiratory test. The respiratory test shown in Fig. 4 brought out a notch due to a change in the direction of rotation of the electrical axis from counterclockwise to clockwise: this curve is not a typical preponderance curve in so far as it does not show uniform rotation of the electrical axis.

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\* An examination of 30 normal curves from this standpoint gave the following results:—  
*R1* plus *R3* equalled *R2* .. .. . 5 instances.

.. .. .	plus or minus	0.1 millivolt	..	16	..
.. .. .	.. .. .	0.15 ..	..	1	..
.. .. .	.. .. .	0.25 ..	..	6	..
.. .. .	.. .. .	0.35 to 0.75 millivolt	..	2	..

*The effects of the position of the heart upon the electrocardiogram in our series of cases.* With the considerations outlined above in mind we have gone over our cases to determine if possible the part played by variations in the position of the heart in causing the observed discordances between the ratio  $L/R$  and the form of the electrocardiogram. In Table V we have tabulated such data as can be given in condensed form. Ascites, aneurism, hydrothorax, and other factors which may cause displacement of the heart are noted. In each case the difference between the sum of the chief deflections of leads  $I$  and  $III$ , and the chief deflection of lead  $II$  is given; it may be taken as a rough measure of the lack of synchronism between the chief peaks, and consequently of the amount of rotation of the electrical axis during the time when the manifest potential difference was near its maximum.\* In about one-half of our cases X-ray plates were available; in each of these instances we have measured the angle between the long diameter of the ventricular shadow and the horizontal.† The interval which elapsed between the X-ray examination and death is given so that the time of the X-ray examination with reference to the time of the electrocardiographic examination is shown. It should be remembered that the X-ray plates were made with the patient in the erect posture, while the electrocardiographic curves were made with the patients in the supine or in the sitting posture. Angles measured on teleröntgenograms are starred.

It would not be profitable to enter into a discussion of the part played by the position of the heart in determining the form of the electrocardiogram in individual cases: in a great many instances no definite opinion can be formed. It may be responsible for many of the minor discordances between the ratio  $L/R$  and the form of the electrocardiogram that we have encountered (see Cases 29 and 55): and it may have exaggerated some of the major discordances. It does not offer a satisfactory explanation of such discordances as occur in Cases 2, 3 and 42. In our opinion it is to be considered but one of many factors which disturb the relation between the form of the  $Q,R,S$  group and the relative weight of the two ventricles.

*Disturbances of intraventricular conduction and the arrangement of the ventricular conducting system.* The aberrant electrocardiograms produced by lesions which prevent the passage of the impulse through one of the chief branches of the His-bundle and their superficial resemblance to preponderance curves require no comment. Recently, we have shown that lesions which delay the passage of the impulse through one of the bundle branches may produce curves which resemble preponderance curves very closely<sup>16</sup>. This

\* In studying our cases with reference to the amount of rotation of the electrical axis shown by the curves, we have not considered this figure by itself; it has been used in connection with inspection of the electrocardiograms.

† The plates were kindly supplied by Dr. Sherwood Moore of Washington University. The measurements were made for us by Dr. J. G. Van Zwaluwenburg of the X-ray Department, University of Michigan.

had previously been suspected by others.<sup>7-11</sup> Fahr advanced the theory that all preponderance curves were produced in this way. He believes that the curves which are now generally attributed to preponderance of the levoecardiogram are in reality due to preponderance of the dextroecardiogram produced by dilatation of the left ventricle and consequent prolongation of the left bundle branch and its arborizations, delaying the passage of the impulse through the left ventricular conducting system. He claims to have made certain measurements of the relative length of the right and left conducting paths, in cases which showed right or left preponderance curves during life, which support his hypothesis. Rothberger and Winterberg<sup>13</sup> have shown that section of the anterior subdivision of the left bundle-branch in the dog produces curves not unlike curves of left ventricular preponderance in man: section of the posterior subdivision of this branch produces curves of more or less opposite type.

It cannot be denied, therefore, that curves similar to those of preponderance may be produced by lesions which interfere with the normal spread of the impulse through the ventricular conducting system. But that all preponderance curves arise in this way cannot be held at present, for the following reasons:—

1. The preponderance curves of the new-born infant cannot be explained on this basis. It may be that the ventricular conducting system of the new-born infant differs from that of the adult; at present, however, we have no foundation for such an assumption.

2. The curves which result from disturbances of intraventricular conduction are almost invariably diphasic when they differ greatly from curves of the normal type. This is more especially the case when *Q.R.S.* is of great amplitude; in leads of very small amplitude *Q.R.S.* and *T* may have the same direction even in complete bundle branch block. Although preponderance curves show a greater tendency to be diphasic than do normal curves, they are often not diphasic, even when of the most exaggerated type (Fig. 5).

3. Although conduction disturbances often give rise to curves of unusually large amplitude, they seldom, if ever, give rise to curves of enormous amplitude such as are sometimes seen in pulmonary stenosis (Fig. 5).

4. Preponderance curves seldom or never develop suddenly. Bundle branch block curves, although they are much less common than preponderance curves, have frequently been observed to develop over night; so far as we know, preponderance curves have never been observed to develop within a brief period of time. They are much more stable than we should expect, if they were due to lesions of the conducting system. Even if they are to be attributed to dilatation of the one or the other ventricle, as Fahr believes, we should expect them to appear or disappear quickly in some cases.

5. The relation of right ventricular preponderance curves to pulmonary stenosis and to mitral stenosis, and of left ventricular preponderance curves to aortic insufficiency and to chronic hypertension, is difficult to explain, if we attribute preponderance curves to disturbances of intraventricular conduction, unless Fahr's hypothesis be adopted.\*

With the hope of gaining some further evidence bearing upon the influence of the relative dilatation of the two ventricles upon the form of the electrocardiogram, we measured the capacity of each ventricle in a number of our cases by a method which has already been described. These measurements are given in Table V. It will be seen at once that the relative dilatation of the two chambers, determined by this method, plays no appreciable part in determining the form of the ventricular complex. It is unquestionably true, however, that the volumes of the ventricular cavities after death bear no definite or constant relation to their volumes during life, when the electrocardiograms are made. We include the measurements, realising that they are of doubtful value, because such measurements have been suggested and because they have a bearing upon the type of measurements that Fahr claims to have made. We include, also, measurements of the thickness of the lateral wall of each ventricle. It will be seen that between these and the measurements of the ventricular capacities there is a sort of reciprocal relation: dilated ventricles have thin walls: contracted ventricles, thick walls.

That lesions of the ventricular conducting system were responsible for lack of agreement between the ratio  $L/R$  and the form of the electrocardiogram in some of our cases is probable; in none of our cases can we feel certain that this was the case. None of the electrocardiograms show definite prolongation of the  $Q.R.S.$  interval: only two show an increase in the  $P-R$  interval, and in both of these it is very slight (Cases 8 and 25). In two instances the electrocardiograms are definitely diphasic (Cases 1 and 42) and conduction defects may have been present in these.

There is a factor related to disturbances of intraventricular conduction that requires discussion here; we refer to the arrangement of the ventricular conducting system. It has been shown<sup>8</sup> that in the dog striking variations in the architecture of the conduction system of the left ventricle occur. That similar variations in the arrangement of the ventricular conducting system occur in man is hardly to be doubted; it is probable that it is upon the architecture of this system that the individuality of the normal electrocardiogram chiefly depends. It seems likely that in most individuals both

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\* This is not the place to discuss Fahr's general hypothesis, that what we now regard as left ventricular effects are in reality right ventricular effects, in detail. It is based almost wholly upon theoretical considerations which we regard as precarious. Fahr has disregarded many facts that are not in accord with his theory: the form of the bundle branch block curves of the "Rhesus monkey," for example. Until he is able to bring his theory more into accord with past observation and until he is able to support it by new experimental evidence, we shall find difficulty in accepting it.

ventricles do not receive the impulse at exactly the same time : in those in which  $Q$  is largest in lead  $III$  and  $S$  in lead  $I$ , the right ventricle may receive the impulse in advance of the left : in other cases the left ventricle precedes the right. In those individuals who normally exhibit curves of the preponderance type, the precedence of one ventricle over the other may be unusually great, although not of the same grade as that seen in pathological cases.

We have already pointed out that the position of the heart has an important influence upon the form of the normal electrocardiogram : its effect is usually combined with that of the arrangement of the ventricular conducting system in such a way that the most important of the two factors cannot be determined. Occasionally, however, this is possible. In Fig. 6 is shown the electrocardiogram of a young woman of unusually stout build : in this instance the form of the electrocardiogram is determined largely by the transverse position of the heart.  $P$ ,  $Q$ ,  $R$ ,  $S$ , and  $T$  are all of small amplitude in lead  $III$  :  $Q$ ,  $R$ ,  $S$ , and  $T$  are inverted. In Fig. 7 the electrocardiogram of a young woman of average build is shown : in this instance the form of the electrocardiogram is determined mainly by precedence of the right ventricle.  $T3$  is inverted here also, but in this instance  $R3$  is tall :  $T$  is largest in lead  $I$ , which shows a conspicuous  $S$  deflection :  $Q$  is present in lead  $III$  alone. The form of  $P$  indicates that the heart is of the pendulous type, but the position of the heart cannot account for the diphasic character of leads  $I$  and  $III$ .

If it be admitted that the arrangement of the ventricular conducting system may be such that one ventricle receives the impulse slightly in advance of the other, then it seems probable that certain individuals develop preponderance curves as a result of alteration of the ratio  $L/R$  more readily than others. If, for instance, some peculiarity of the conducting system gives rise in a certain individual to curves which suggest slight right ventricular preponderance, it will probably take a much greater relative preponderance of the left ventricular muscle to produce the signs of left ventricular preponderance, than in an individual with a conducting system of the opposite type. Our knowledge is insufficient, however, to determine how these two factors, the arrangement of the conducting system and the relative weight of the two ventricles, will react with one another under various conditions.

*Discussion of individual cases.* To explain satisfactorily the lack of agreement between the ratio  $L/R$  and the form of the ventricular complex in individual cases is difficult or impossible. It would be unprofitable, therefore, to discuss a large number of our cases in detail. We have selected four of the important ones for special comment.

Case 2.  $L/R$  ratio, 3.59. Electrocardiogram shows no left ventricular preponderance (Fig. 8A). The patient, a girl aged 14, was under observation from May 27th, 1920, until death, July 9th, 1920. During this period

four electrocardiograms were made; all of these are very much alike, except that the later ones show inversion of *T* due to the administration of digitalis. The final curve was taken 20 days before death, and it seems unlikely that any change in the ratio *L/R* took place during this period: the symptoms had been present for about one year. The heart was definitely enlarged (apex 14 cm. from the midline) and hypertrophied (ventricular-weight/body-weight ratio, 0.00590). There was no cause for cardiac displacement except a small collection of pus in the right pleural cavity. The electrocardiogram is of the normal type and does not suggest wide rotation of the electrical axis during the inscription of *R*, which is notched in lead *I*. The curves show no evidence of conduction defects. The failure of the electrocardiogram to show left ventricular preponderance is difficult to explain.

Case 3. *L/R* ratio, 2.86. Electrocardiogram shows no left ventricular preponderance (Fig. 8B). The patient was under observation from February 27th, 1920, until death, June 6th, 1920. During this period a number of electrocardiograms were taken; all of these are practically identical in form. Examination of the patient on admission showed no cardiac enlargement; there was aortic insufficiency due to a streptococcus viridans endocarditis. The patient grew worse gradually, but did not develop heart failure until near the end of his illness. The last curve was made 38 days before death, and it is possible that there was some change in the ratio *L/R* after this examination. The X-ray examination showed a long tortuous aorta and a transverse ventricular shadow, so that the position of the heart cannot be held responsible for the failure of the electrocardiogram to show left ventricular preponderance. The curves show no evidence of conduction defects; they are normal in all respects, and are of the type which suggests slight precedence of the right ventricle. We are inclined to attribute the lack of agreement between the ratio *L/R* and the form of the electrocardiogram in this instance to the slight degree of ventricular hypertrophy present, to change in the ratio *L/R* after the last electrocardiographic examination, and to the arrangement of the ventricular conducting system.

Case 42. *L/R* ratio, 1.65. Electrocardiogram shows definite left ventricular preponderance (Fig. 8c). This patient was under observation from August 17th, 1920, until death, September 13th, 1920. Two curves were made; these are very much alike, except that the final one shows a curious notching of *T*; it was taken one day before death. There was no cause for displacement of the heart, and the form of the curves could not, in any case, be explained on this basis. They are diphasic, and suggest considerable rotation of the electrical axis. The *Q.R.S.* and *P-R* intervals are within normal limits. We are inclined to attribute these curves to conduction defects or to an unusual arrangement of the ventricular conducting system.

Case 54. *L/R* ratio, 1.45. Electrocardiogram shows definite left ventricular preponderance (Fig. 8d). This patient was admitted to the



hospital on four different occasions: two electrocardiograms were made, the final one 63 days before death, the other about one year earlier. Both indicate definite left ventricular preponderance. The curves are of the type associated with a nearly horizontal major electrical axis, and they do not suggest wide rotation of the electrical axis during the inscription of the chief deflections. They are not diphasic: *T* is inverted in lead *III*. *Q.R.S.* of lead *III* is deeply notched toward the end of the *Q.R.S.* interval. There were ascites and tympanites at the time of the last examination. It is possible that a transversely placed heart was in part responsible for the form of the electrocardiogram. The form of *P*, which is taller in lead *III* than in lead *I*, and the large amplitude of *Q.R.S.* is somewhat against this view. An unusual arrangement of the ventricular conducting system may have been a contributory factor.

*Remarks upon indices.* During the last few years, a belief that there is a close relation between the form of the electrocardiogram and the ratio *L R* has led several observers to advocate the use of numerical indices to express the degree of right or left ventricular preponderance shown by the electrocardiogram. White and Boek<sup>15</sup> advocate an index similar to the one used in this article. Carter and Greene<sup>1</sup> prefer an index based upon Einthoven's equilateral triangle: their index is intended to express in degrees the position of the major electrical axis: whether it does so or not need not be discussed here. We have computed this index in each of our cases; it is given in Table V. None of the indices so far proposed are of any precise value in distinguishing between the effects of rotation of the heart and of conduction defects, on the one hand, and the effects of an abnormal *L R* ratio, on the other. They are greatly inferior to simple inspection of the electrocardiogram.

### *Conclusions.*

The relative weight of the two ventricles is but one of many factors which influence the form of the ventricular complex of the electrocardiogram. Its influence predominates only when the heart is greatly hypertrophied. There is no definite relation between the form of the ventricular complex and the relative weight of the two ventricles when the ventricular weight is below 250 grams.

The chief factors which disturb the relation between the form of the electrocardiogram and the relative weight of the two ventricles, so it is suggested, are: (1) variations in the position of the heart, (2) variations in the arrangement of the ventricular conducting system, and (3) disturbances of intraventricular conduction.

The form of the normal electrocardiogram is not determined by the relative weight of the two ventricles: it is chiefly dependent upon the position of the heart and upon the arrangement of the ventricular conducting system; sometimes one, sometimes the other, of these factors exerts the greater influence.

TABLE I.—*Pathological findings.*

No.	Case No.	Age, Sex.	Height cm.	Weight kilos	Heart Weight gms.	Vent. Weight gms.	R	L	S	L R	Ratio Vent. Wt. Body Wt
1	58	39 M	165	54	537	387	64.7	247.6	75.0	3.83**	0.00719
2	22	14 F	145	30	290	177	31.9	114.6	30.0	3.59	0.00590
3	19	47 M	175	57	420	224	48.8	139.9	35.2	2.86	0.00394
4	48	35 M	167	57	520	351	74.7	210.5	65.6	2.82*	0.00615
5	3	32 M	175	75	700	391	85.9	232.5	72.3	2.72***	0.00521
6	47	38 M	176	62	615	334	77.3	202.4	53.8	2.62*	0.00538
7	37	60 F	160	38	168	91	21.9	56.4	13.1	2.57	0.00236
8	1	78 F	135	34	540	158	36.3	92.0	29.3	2.53*	0.00465
9	33	60 F	162	40	385	194	45.1	113.0	36.0	2.50	0.00485
10	36	76 M	183	43	205	130	32.0	79.3	18.7	2.48**	0.00302
11	7	48 M	157	45	700	427	105.0	259.4	62.6	2.46**	0.00950



TABLE 1.—Pathological findings.

Valvular Defects.	Kidney Lesions.	B.P. Systolic.	B.P. Diastolic.	Remarks.
None.	R. 210 gms. L. 215 gms. Surface sl. granular. Chr. nephritis.	240	160	Sclerosis of coronaries. Alb. retinitis. Chr. uræmia.
None.	R. 103 gms. L. 52 gms. Small granular kidneys.	275	190	Mural thrombi. Ball throm- bus in aorta. Alb. retinitis. Empyema (Rt.).
Vegetations on aortic and mitral flaps. Aort. re- gurg. (S. viridans)	R. 200 gms. L. 210 gms. Acute and chronic nephr.	132	58	Aortitis with early aneurism (s. viridans). Ac. and chr. pericarditis. Mural throm- bus.
None.	R. 80 gms. L. 80 gms. Small red gran. kidneys.	228	150	Great coronary scl. Scl. of peripheral arteries. Alb. retinitis. Uræmia.
None.	Chr. degenerative parenchy- matous nephr.	185	140	Fibrino-purulent pericarditis and pleurisy. Alb. reti- nitis. Uræmia. Anasarca.
Small well-organised vege- tation on aortic cusp. No regurg.	R. 180 gms. L. 140 gms. Arterioscl. gran. kidneys.	265	145	General arterioscl. Alb. reti- nitis.
None.	R. 100 gms. L. 110 gms. Chr. diffuse nephr. with cysts. Arterioles very sclerotic. Many fibrotic glomeruli. Very little increase in interstitial tissue.	118	75	Considerable scl. of aorta and peripheral arteries. Ascites.
None.	R. 125 gms. L. 155 gms. Hydronephrosis (left).	170	110	Syphilitic aortitis with large aneurism. Heart con- siderably displaced. Aur. flutter and fib. General arterioscl.
Fresh vegetations on aortic cusps. No regurg.	R. 480 gms. L. 255 gms. R. pyonephrosis. L. hy- pertrophy.	180	100	Mod. scl. of aorta and of coronary arteries.
Mitral flaps and aortic cusps thickened. Mitral regurg.	R. and L. 275 gms. Arte- rioscl. changes in vessels and fibrosis of many glomeruli.	140	70	Mod. atheroma of aorta. Some calc. of aorta. Em- physema of lungs. Ascites.
Ac. and chr. vegetative endocarditis involving mitral, aortic and tri- cuspid segments (s. viri- dans). Aortic regurg.	R. and L. each 120 gms. Arteriosclerotic nephritis.	180	75	Aorta atheromatous. Car- diac failure. Transient aur. fib.

TABLE 1. *Pathological findings (continued).*

No.	Case No.	Age, Sex	Height cm.	Weight lbs.	Heart Wt. gms.	Vent. Wt. gms.	R	L	S	L/R	Ratio Vent. Wt. Body Wt.
12	9	44 M	185	64	305	163	39.4	96.7	26.5	2.46	0.00255
13	24	48 F	161	34	285	101	26.2	61.8	12.4	2.36	0.00302
14	6	57 M	175	48	315	181	48.2	108.7	24.6	2.25 <sup>0</sup> *	0.00378
15	10	59 M	165	48	300	146	37.8	85.0	23.0	2.25	0.00305
16	31	75 F	145	30	285	128	34.0	74.7	19.3	2.20	0.00427
17	40	37 F	150	55	480	276	74.6	164.8	36.4	2.20*	0.00500
18	41	49 M	160	58	350	163	45.6	97.5	20.0	2.14**	0.00284
19	51	58 M	162	45	360	140	39.3	79.6	20.8	2.02	0.00311
20	52	68 M	178	72	408	178	50.8	101.1	26.3	1.99	0.00248
21	26	17 F	146	40	235	157	44.3	87.0	25.4	1.97	0.00394

TABLE I.—*Pathological findings (continued).*

Valvular Defects.	Kidney Lesions	B P Systolic.	B P Diastolic.	Remarks
Patent foramen ovale. Sl. fenestration of pulmonary segments.	R. 205 gms. L. 190 gms. Congestion and acute degenerative changes.	160	70	Slight thickening at base of aorta. Sl. hæmorrhage into ventricular septum. Thromb. rt. pul. art.
None.	R. and L. 940 gms. Capsule adherent, surface granular. Sl. increase in interstitial tissue.	110	70	Aorta atheromatous. 100 c.c. pericardial fluid. Ascites. Hydrothorax (Lf.). Pernicious anemia.
None.	R. 130 gms. L. 260 gms. Bilateral hydronephrosis. Great increase in interstitial connective tissue.	260 140	110 75	Advanced general sclerosis and calc. of coronaries. Chr. uræmia. Cancer of prostate.
None.	R. 150 gms. L. 155 gms. Surface very granular, capsule adherent. Many scars.	140	70	General arteriosclerosis. Diabetes mellitus. Ventricular extrasystoles.
Aortic and mitral segments thickened. Calc. nodule in one aortic segment.	R. 100 gms. L. 95 gms. Caps adherent. Surface slightly granular. Inc. interst. tissue. Vessels scl.	200 130	75 40	Great scl. of aorta. Coronaries sclerotic and left narrowed. Endarteritis obliterans (feet).
Sl. mitral and sl. tricuspid regurg. by hydrostatic test.	R. 140 gms. L. 150 gms. Scl. of small arterioles. Acute tubular nephr. Congestion and ac. degenerative changes.	126	65	Mural thrombi in left ventricle. Infarction of lungs. Pleural effusion.
Slight atheroma of aortic cusp.	R. 200 gms. L. 190 gms. Sl. atheroma of vessels. Fatty degeneration.	125	90	Aorta atheromatous. Ascites. Cancer of liver. Hemochromatosis.
None.	Kidneys of normal size. Fibrosis of many glomeruli. Increase in interstitial tissue.	110	78	— — —
Aortic and mitral segments thickened. Some calc. of latter.	R. 110 gms. L. 120 gms. Surface granular. Many fibrotic glomeruli. Gre. increase of connective tissue. Vessels very scl.	158	68	Advanced sclerosis of aorta and peripheral arteries. Cancer of stomach.
Chr. endocarditis involving aortic, mitral, and tricuspid segments. Acute vegetations (Rheumatic). Mitral, aortic and tricuspid regurg.	R. 140 gms. L. 110 gms. Congestion and edema.	110	35	Sl. sclerosis of aorta. Cardiac failure. Hydrothorax. Ascites.

TABLE I. *Pathological findings (continued).*

No.	Case No.	Age, Sex.	Height cm.	Weight kilos.	Heart Wt. gms.	Vent. Wt. gms.	R	L	S	L/R	Ratio Vent. Wt. Body Wt.
22	13	70 F	157	49	340	160	44.0	86.3	30.0	1.96**	0.00327
23	44	41 F	180	79	280	138	37.6	73.7	26.7	1.96	0.00175
24	29	71 M	161	66	600	323	91.6	177.7	54.1	1.94**	0.00490
25	18	63 M	157	71	700	372	104.7	202.7	65.0	1.94**	0.00525
26	8	17 M	175	36	210	119	32.7	63.2	22.7	1.93	0.00331
27	54	56 F	150	35	225	119	33.7	64.6	20.8	1.92	0.00340
28	49	33 F	158	48	320	185	58.1	106.5	20.6	1.83	0.00390
29	57	26 F	160	35	187	107	33.1	60.3	13.3	1.82*	0.00306
30	35	33 F	159	33	280	152	46.0	82.7	23.3	1.80	0.00461
31	11	63 M	161	37	250	111	33.0	59.5	18.7	1.80	0.00300
32	30	34 M	178	53	305	173	53.8	95.3	24.0	1.78	0.00326
33	46	54 F	165	50	205	87	27.0	47.6	12.8	1.75	0.00174
34	34	38 M	157	43	225	159	49.5	85.0	24.0	1.71	0.00370

TABLE I.—Pathological findings continued.

Valvular Defects.	Kidney Lesions.	B.P. Systolic.	B.P. Diastolic.	Remarks.
Mitral and aortic segments thickened. Mitral regurg.	R. 170 gms. L. 190 gms. Surface granular. Vessels sclerosed. Increased connective tissue.	150	60	Coronaries sclerotic and calcified. Cardiac failure. Aur. fib. Gen. arterioscl. Sero-purulent pericarditis.
None.	R. and L. 420 gms. Essentially negative.	90	65	General peritonitis.
None.	R. 150 gms. L. 165 gms. Capsule adherent. Surface granular. Vessels sclerosed. Inc. connective tissue.	150	100	Coronaries atheromatous. Hydrothorax, ascites. Chr. passive congestion.
Some calcification about mitral and tricuspid rings.	R. 150 gms. L. 170 gms. Red granular surface.	200 185	140 115	Sl. atheroma of aorta. Partial heart-block. Albuminuric retinitis. General anasarca.
None.	R. 110 gms. L. 120 gms. Acute degenerative changes.	118	90	Polio-encephalitis. Bronchopneumonia.
None.	R. and L. 220 gms. Congested only.	140	104	Moderate sclerosis of vessels.
None.	R. and L. 300 gms. Congestion and cloudy swelling.	130 145	100 110	Post-partum infarction of lungs.
Sl. thickening of one mitral segment. No regurg.	R. and L. 220 gms.	100 94	65 70	—
Patent foramen ovale. Open ventricular septum. Vent. opening 6 mm. in diameter.	R. 200 gms. L. 220 gms. Suppurative nephritis with multiple abscesses. Chr. glomerular nephr.	148	70	Aorta normal. Fibrinous pericarditis. Uræmia.
Slight thickening of mitral segments.	R. 105 gms. L. 110 gms. Chr. interstitial nephr. Vessels thickened. Some scarring.	150 140	90 75	General arterioscl. Coronaries sclerotic. Cancer of œsophagus and rectum.
Sl. fenestration of aortic and pulmonic segments.	R. 140 gms. Cloudy swelling.	115	65	Otitis media, brain abscess. Empyema (left).
None.	R. 160 gms. L. 150 gms. Acute degenerative changes.	115	75	Cancer of mammary gland.
None.	R. 130 gms. Cloudy swelling.	118	94	Cancer of stomach. Ascites.

TABLE 1. *Pathological findings (continued).*

No.	Case No.	Age, Sex.	Height cm.	Weight kilos.	Heart Wt. gms.	Vent. Wt. gms.	R	L	S	L/R	Ratio Vent. Wt. Body Wt.
35	21	16 M	153	37	230	139	43.1	73.5	22.5	1.70**	0.00376
36	25	46 M	147	51	305	147	46.9	80.0	20.0	1.70	0.00289
37	32	31 M	175	52	400	193	60.7	103.5	29.1	1.70	0.00371
38	59	19 M	170	—	261	160	49.2	83.6	26.9	1.70	—
39	53	22 M	174	61	279	200	63.9	107.8	28.6	1.69	0.00328
40	4	14 M	152	36	225	115	36.2	60.3	18.3	1.67	0.00320
41	27	70 M	167	39	295	121	38.2	63.2	19.3	1.66	0.00310
42	28	63 M	147	63	245	107	35.1	57.9	14.3	1.65**	0.00170
43	42	46 M	162	68	285	146	47.9	76.9	20.8	1.61	0.00215
44	55	35 M	172	—	332	215	71.6	115.4	27.6	1.61	—
45	38	52 M	180	53	260	137	43.7	69.9	23.6	1.60	0.00259
46	17	52 M	167	45	365	157	47.5	74.8	34.2	1.58	0.00349
47	14	0.6 F	58	3.4	30	18	6.0	9.5	2.5	1.58	0.00530

TABLE I.—*Pathological findings (continued).*

Valvular Defects.	Kidney Lesions.	B.P. Systolic.	B.P. Diastolic.	Remarks.
None.	<i>R. and L. each 120 gms.</i> Congestion and cloudy swelling.	100	86	Cerebrospinal meningitis. Bronchopneumonia.
Sl. thickening of mitral and aortic segments.	<i>R. 150 gms. L. 210 gms.</i> Hyalin change in small vessels.	145	90	Syphilitic aortitis with large aneurism involving innominate. Cirrhosis of liver.
Mitral and tricuspid regurg. (relative).	<i>R. and L. 200 gms.</i> Fatty degeneration.	100	50	Fatty degeneration of myocardium. Pernicious anemia.
None.	<i>R. and L. 230 gms.</i>	105	70	Miliary tuberculosis.
Sl. thickening of mitral segments.	<i>R. and L. 430 gms.</i> Tissue- tially negative.	130	80	Empyema (right). Osteomyelitis of inf. maxilla.
None.	<i>R. 270 gms. L. 280 gms.</i> Cloudy swelling. Leukæmic changes.	110	75	Acute lymphatic leukæmia.
Dilatation of aorta with questionable relative aortic regurg.	<i>R. 150 gms. L. 200 gms.</i> Chr. interstitial nephr. Vessels sclerotic. Considerable scarring.	150	67	Atheromatous dilated aorta. Emphysema. Pleural effusion. Tbc. pneumonia.
None.	<i>R. 125 gms. L. 130 gms.</i> Sl. increase in connective tissue. Hyalin change in vessels.	140	70	Append. abscess. General peritonitis.
None.	<i>R. 185 gms. L. 160 gms.</i> A few sclerotic glomeruli. Perivascular infiltration.	140 125	85 100	Thrombosis of cavernous sinus.
None.	<i>R. and L. 565 gms.</i>	90 115	50 68	Pernicious anemia.
Valve segments thickened. Rel. mitral and tricuspid regurg. by hydrostatic test.	<i>R. and L. 225 gms.</i> Cloudy swelling. Some sclerosis of vessels.	90	50	Adeno-carcinoma of stomach.
None.	<i>R. and L. each 140 gms.</i> Chr. nephritis. Advanced degeneration of tubular epithelium.	142	90	Aorta atheromatous. Glioma of VII nerve.
None.	<i>R. 32 gms. L. 32.5 gms.</i> Acute glomerular and interstitial nephr.	95	75	Erysipelas. Syphilis.

TABLE I. *Pathological findings (continued).*

No.	Case No.	Age, Sex.	Height cm.	Weight kilos.	Heart Wt. gms.	Vent. Wt. gms.	R	L	S	L R	Ratio Vent. Wt. Body Wt.
48	5	45 F	150	35	325	184	60.5	95.2	28.7	1.58	0.00525
49	45	25 F	163	50	330	167	58.5	91.1	17.5	1.56	0.00334
50	12	64 M	175	53	320	166	56.5	88.3	21.6	1.56	0.00314
51	39	55 M	185	57	360	186	64.1	96.8	25.3	1.51	0.00330
52	60	18 M	170	37	207	132	45.3	67.9	19.2	1.51	0.00351
53	50	34 F	160	43	265	145	50.4	73.7	20.7	1.46	0.00342
54	20	43 F	165	67	400	199	71.2	101.6	26.2	1.45**	0.00297
55	2	49 M	163	58	340	170	61.9	87.9	20.0	1.42	0.00293
56	43	61 M	166	41	260	125	45.1	62.3	17.7	1.38	0.00305
57	56	43 M	172	52	326	208	80.7	96.3	30.7	1.19	0.00400
58	23	21 M	167	48	580	261	107.3	120.2	33.3	1.12	0.00545
59	16	32 F	154	65	350	149	68.2	66.0	14.7	0.96	0.00230



TABLE 1. *Pathological findings (continued).*

Valvular Defects.	Kidney Lesions.	B.P. Systolic.	B.P. Diastolic.	Remarks.
None.	R. 170 gms. L. 195 gms. Cloudy swelling.	120	50	Multiple infected myomata of uterus. General arteriosclerosis. Empyema. Bronchopneumonia.
Subacute endocarditis involving mitral and aortic segments. Aortic regurg. (s. viridans).	R. 140 gms. L. 150 gms. Acute nephritis.	115	75	Cardiac failure. General anasarca. Ascites. Hydrothorax.
Thickening of aortic segments. No regurg.	R. 140 gms. L. 175 gms. Bilateral hydronephrosis.	145	85	Coronaries sclerotic. Old syphilis. Cardiac failure. Aur. fib. Vent. extrasystoles.
None.	R. 230 gms. L. 240 gms. Congestion.	140 115	82 70	Chr. adhesive pericarditis. Transient aur. fib. Adenocarc. of stomach.
None.	R. and L. 250 gms.	100 140	70 80	Dementia præcox. Perforation of œsophagus. Bronchopneumonia. Pneumothorax.
None.	Cloudy swelling. Edema of interstitial tissue.	124 138	70 70	Bronchopneumonia.
None.	R. 150 gms. L. 160 gms. Cloudy swelling.	105	68	Aorta atheromatous. Aleukemic leukaemia. Fatty degeneration of the heart muscle. Ascites. Severe anemia.
None.	Advanced parenchymatous degeneration.	120	90	Syphilitic aortitis with large aneurism.
Sclerosis and calc. of aortic segments. No aortic regurg.	R. and L. 520 gms. Acute tubular nephritis.	120	90	Sl. sclerosis of pulmonary artery. General arteriosclerosis.
Sl. tricuspid regurg. by hydrostatic test.	R. and L. 450 gms. Congestion.	140 125	80 80	Massive Tbc. of lungs. General miliary Tbc.
Mitral stenosis. Mitral and aortic regurg. A few small vegetations.	Chronic passive cong.			Cardiac failure. Auricular fibrillation. A few pericardial adhesions.
None.	Sarcoma of left kidney (small). Acute parenchymatous nephritis.	140	88	Very advanced chronic pulmonary emphysema.

TABLE II.—*Electrocardiographic measurements.*

No.	Case No.	Age, Sex	Vent. AVE. gms.	L.R	Index.	Interval E.C.G. to death, days	<i>P</i> 1	<i>P</i> 2	<i>P</i> 3	<i>q</i> 1	<i>q</i> 2	<i>q</i> 3
1	58	39 M	387	3.83	33.0**	1	T	1.0	1.0	1.0	0.0	0.0
2	22	14 F	177	3.59	5.5	20	0.5	1.0	0.5	0.0	T	1.0
3	19	47 M	224	2.86	-4.0	38	T	0.5	0.5	0.0	1.0	1.5
4	18	35 M	351	2.82	3.5*	7	1.0	T	-0.5	0.0	0.5	1.0
5	3	32 M	391	2.72	14.0* 2.5	10 8	1.0 0.5	1.0 1.5	±T 1.0	0.0 0.0	0.0 0.0	0.0 0.0
6	47	38 M	334	2.62	16.0*	3	1.5	3.0	2.0	0.0	0.0	0.0
7	37	60 F	91	2.57	2.5	60	T	T	T	0.0	0.5	1.0
8	1	78 F	158	2.53	7.5*	5	T	1.5*	1.5*	T	0.0	0.0
9	33	60 F	194	2.50	9.0	20	T	1.0	0.5	0.0	0.0	0.0
10	36	76 M	130	2.48	10.0** 6.5*	6 3	T T	0.5 0.5	0.5 1.0	0.5 0.5	0.0 0.0	0.0 0.0
11	7	48 M	427	2.46	17.8**	15	0.5	1.0	±0.5	0.0	0.0	0.0
12	9	44 M	163	2.46	-3.0	0	1.0	2.0	1.0	0.0	0.0	0.5
13	24	48 F	101	2.36	-6.0	1	T	1.0	1.0	0.0	0.0	T
14	6	57 M	181	2.25	7.0* -3.5	20 2	T T	1.5 2.0	1.0 2.0	0.5 T	0.0 2.0	0.0 2.0
15	10	59 M	146	2.25	3.5	8	T	0.5	0.5	0.0	1.0	1.0
16	31	75 F	128	2.20	0.0	21	T	0.5	0.5	0.0	1.0	1.0
17	40	37 F	276	2.20	7.0*	12	T*	1.0	1.0	0.0	0.0	0.0
18	41	49 M	163	2.14	12.5**	1	1.0	1.5	1.0	T	0.0	0.0
19	51	58 M	140	2.02	4.0	0	1.0	2.0	1.0	T	0.5	0.5
20	52	68 M	178	1.99	7.5	0	0.6	0.6	-T	0.0	0.0	0.0
21	26	17 F	157	1.97	1.0	4	0.5	1.0	0.5	0.5	0.5	1.0
22	13	70 F	160	1.96	17.0**	1	1.5	2.0	1.0	T	1.0	0.0
23	44	41 F	138	1.96	0.5	5	0.5	1.5	0.5	0.0	1.0	1.0
24	29	71 M	323	1.94	9.5**	6	T	1.0	0.5	0.0	0.0	0.0
25	18	63 M	372	1.94	16.5**	6	T	1.0	1.0	T	0.0	0.0
26	8	17 M	119	1.93	7.0	30	0.5	1.5	1.0	0.0	0.0	T
27	54	56 F	119	1.92	5.5	34	0.5	1.5	1.0	T	0.0	0.0
28	49	33 F	185	1.83	1.5	14	0.5	1.0	T	0.0	0.0	T
29	57	26 F	107	1.82	-13.0*	49	0.5	1.0	T	0.0	0.5	2.0
30	35	33 F	152	1.80	8.0	43	T	2.0	1.5	0.0	0.0	0.0

\* Electrocardiographic measurements are so marked to indicate that the corresponding deflections were

\*\* Indices are so marked to indicate that the corresponding electrocardiograms show certain signs of right

TABLE II.—*Electrocardiographic measurements.*

<i>R1</i>	<i>R2</i>	<i>R3</i>	<i>S1</i>	<i>S2</i>	<i>S3</i>	<i>T1</i>	<i>T2</i>	<i>T3</i>	Disease.
19.0	11.0	5.0	0.0	6.0	19.0	-3.0	±1.0	2.0	Chronic nephritis.
6.0*	7.0	2.0*	0.5	1.0	2.0	T	-2.0	-2.0	Chronic nephritis.
4.0	9.0	6.5	2.0	1.0	0.5	1.5	1.5	T	Sub-acute bacterial endocarditis.
11.0	9.0	6.0*	1.5	0.0	0.0	-1.5	-1.5	-1.0	Chronic nephritis.
8.0	6.0	0.5	0.0	1.5	6.5	0.5	2.0	1.0	Chronic nephritis.
4.0	6.0	3.0	0.5	1.0	2.0	0.5	2.5	2.0	
11.0	13.0	6.0	T	2.5	11.0	T	2.5	2.5	Chronic nephritis.
4.0	5.0	1.5*	0.0	0.0	0.0	T	-T	-T	Cancer of hepatic duct.
3.5*	8.5	7.0	0.0	8.5	11.0	±T	1.5	1.0	Cancer of bladder.
6.5	7.0	0.0	0.0	1.0	2.5	-T	T	1.0	Aneurism.
6.0	1.0*	1.0	0.0	0.0	5.0	T	T	T	Diabetes, pyonephrosis.
5.0	3.0*	1.0	0.0	0.0	2.5	-T	-0.5	-T	Thrombosis of portal vein.
13.0	6.0	1.2	1.0	2.0	7.0*	-0.5	0.5	-T	Vegetative endocarditis.
6.0	8.0	8.0	1.0	0.0	0.0	1.0	2.0	1.5	Aortic regurg.
1.0	9.0	7.0	0.0	0.0	0.0	0.5	1.5	1.5	Purpura, pneumonia.
4.5	6.0	4.0	0.0	3.0	6.5	T	3.0	3.0	Pernicious anæmia.
3.5	10.0	7.0	0.0	0.0	0.0	T	4.5	4.5	Cancer of the prostate.
7.0	11.0	8.5	2.0	0.0	0.0	1.5	3.0	3.0	Diabetes, syphilis.
7.0	13.0	7.0	0.0	0.0	0.0	-T	-1.5	-1.0	Cancer of uterus.
4.0*	4.5	3.0*	0.0	2.0	6.0	T	-1.0	-1.0	Paratyphoid B. ileocolitis.
6.0	3.0	2.5	0.0	4.5	9.0	1.0	2.5	2.0	Cancer of liver.
6.0	5.0	1.5	0.5	1.0	T	T	T	-T	Cancer of the œsophagus.
5.5	3.5	0.0	0.0	0.0	2.0	1.8	1.0	-1.0	Cancer of stomach.
4.5	7.0	4.5	0.5	2.0	1.5	2.0	2.0	T	Aortic regurg. and mitral regurg.
10.0	5.0	0.0	0.0	0.0	7.0	T	T	T	Diabetes mellitus.
7.5	14.0	6.0	1.0	1.0	T	T	T	T	General peritonitis.
6.0	3.0	1.5	1.0	1.0	6.0	-T	-1.0	T	Chronic nephritis.
9.5	3.0	1.5	2.0	6.0	10.5*	T	T	T	Chronic nephritis.
8.0	12.0	4.0	2.0	7.0	5.0*	T	2.0	1.5	Epidemic encephalitis.
8.5	15.0	6.5	0.0	0.0	3.5	T	-T	-T	Cancer of stomach.
6.5	9.5	4.0	1.0	1.0	T	-0.5	T	T	Post-partum thrombosis of pulmonary artery.
2.0	6.5	10.0	5.0	2.0	0.0	1.0	T	-0.5	Cancer of lung.
7.0	8.0	2.0	T	1.5	3.0	0.5	0.5	T	Pyelonephritis.

notched.

or left ventricular preponderance described in the text.

TABLE II.—*Electrocardiographic measurements (continued).*

No.	Case No.	Age, Sex.	Vent. rate.	L/R	Index.	Interval E.C.G. to death, days.	P1	P2	P3	Q1	Q2	Q3
31	11	63 M	111	1-80	6-0 1-0	44 18	T T	1-0 1-0	T T	1-0 1-0	1-0 1-0	1-5 0-0
32	30	34 M	173	1-78	4-0	3	1-0	2-5	2-0	0-5	1-0	T
33	46	54 F	87	1-75	5-0	6	1-0	0-5*	T	1-0	1-5	1-5
34	34	38 M	159	1-71	0-5	0	T	0-5	0-5	0-5	T	T
35	21	16 M	139	1-70	-18-5**	3	0-5	1-5	1-0	0-0	0-0	0-0
36	25	46 M	147	1-70	-6-5	9	T	3-0	2-5	0-0	0-0	0-0
37	32	31 M	193	1-70	9-0 5-5	81 38	0-5 0-5	1-5 1-0	1-0 1-0	1-0 0-5	1-0 0-5	0-0 0-0
38	59	19 M	160	1-70	11-0	6	0-5	1-8	1-0	0-0	1-0	2-0
39	53	22 M	200	1-69	-2-5	11	0-5	1-0	T	0-0	0-0	2-0
40	4	14 M	115	1-67	2-0	3	0-5	0-5	0-5	T	T	0-0
41	27	70 M	121	1-66	-2-5	36	T	1-0	1-0	0-0	0-0	T
42	28	63 F	107	1-65	18-0**	1	1-0	1-5	0-5	0-5	0-0	0-0
43	42	46 M	146	1-61	-1-0	5	0-5	1-0	$\pm 0-5$	0-0	0-0	1-0
44	55	35 M	215	1-61	3-5	3	T	1-2	1-0	T	0-5	T
45	38	52 M	137	1-60	0-0	14	T	1-5	1-5	0-0	T	0-0
46	17	52 M	157	1-58	-4-0	2	0-0	1-0	1-0	0-0	T	T
47	14	0-6 F	18	1-58	-4-5	18	1-0	1-5	0-5	T	1-0	2-0
48	5	45 F	184	1-58	6-5	12	T	2-0	1-5	0-0	0-0	T
49	45	25 F	167	1-56	1-0	6	1-0	1-0	T	1-0	0-5	0-0
50	12	64 M	166	1-56	-3-0	1	<i>Aur. F1 b.</i>			0-0	1-0	1-0
51	39	55 M	186	1-51	-5-0	3	0-5	1-5	1-0	0-0	0-0	T
52	60	18 M	132	1-51	6-5	1	0-5	1-5	1-0	T	0-0	T
53	50	34 F	145	1-46	0-5	0	1-0	1-0	T	T	1-5	1-0
54	20	43 F	199	1-45	26-5**	63	T	1-5	1-5	2-0	0-0	0-0
55	2	49 M	170	1-42	2-5 3-5	3 647	$\pm$ T 1-0	$\mp$ T* 2-0	$\mp$ T* 1-5	T 0-5	0-0 0-0	0-0 0-0
56	43	61 M	125	1-38	2-5	58	T	1-0	1-0	1-0	1-0	0-0
57	56	43 M	208	1-19	-8-0	14	0-5	2-5	2-0	0-0	1-0	1-0
58	23	21 M	261	1-12	7-0	1	<i>Aur. F1 b.</i>			0-0	0-0	T
59	16	32 F	149	0-96	-6-0	73	T	3-0	2-5	0-0	1-0	2-0

\* Electrocardiographic measurements are so marked to indicate that the corresponding deflections were

\*\* Indices are so marked to indicate that the corresponding electrocardiograms show certain signs of right

TABLE II.—*Electrocardiographic measurements (continued).*

<i>R1</i>	<i>R2</i>	<i>R3</i>	<i>S1</i>	<i>S2</i>	<i>S3</i>	<i>T1</i>	<i>T2</i>	<i>T3</i>	Disease.
8.0 6.0	9.0 12.0	2.0 5.0	0.0 0.0	0.0 0.0	0.0 0.0	T T	T T	T T	Cancer of the oesophagus.
4.0	11.0	8.0	T	0.5	0.0	2.0	5.0	3.0	Mastoiditis, meningitis.
8.0	10.0	2.0	1.0	0.0	0.0	1.5	1.0	T	Cancer of breast.
2.5	3.5	2.0*	0.0	0.0	0.0	T	0.5	0.5	Cancer of stomach.
2.0	11.0	15.5	7.5	3.0	2.5	2.0	4.0	3.5	Cerebrospinal meningitis.
4.0	12.0*	9.5*	1.0	0.0	0.0	T	2.0	2.0	Aortic aneurism.
11.0 7.0	12.0 8.0	2.0 1.5	0.0 0.0	0.0 0.0	0.0 0.0	- 0.5 0.5	- 1.0 1.0	- T 0.5	Pernicious anæmia.
3.0	12.0	12.0	2.0	1.0	0.0	1.0	3.0	2.0	Miliary tuberculosis.
7.0	9.0	4.5	5.0	4.0	T	1.5	1.0	T	Osteomyelitis of jaw, septicæmia.
9.0	8.5	5.0*	2.5	1.0	0.5	3.0	3.0	1.0	Lymphatic leucæmia.
3.0	7.0	7.0	T	1.0	1.5	0.5	1.5	1.0	T.b.c. pneumonia.
12.0	3.0	1.0	0.0	2.0	7.0	$\pm 1.0$	1.0*	2.0*	General peritonitis.
6.0	7.0	5.0*	2.5	2.0	0.5	1.5	T	- 1.0	Thrombosis of the cavernous sinus.
4.0	12.0	7.5	0.0	0.0	0.0	T	- 1.0	- 0.8	Pernicious anæmia.
4.0	8.0	4.0	1.0	2.0	1.0	1.0	1.0	0.5	Cancer of stomach.
3.0	11.0	7.0	2.0	3.0	2.0	1.5	2.5	1.5	Glioma of VIII nerve.
5.5	12.0	7.0	3.0	2.0	0.0	3.5	2.5	- 1.5	Erysipelas. Congenital syphilis.
7.0	7.0	1.5*	0.0	0.0	1.0	1.0	1.0	T	Infected myomata of the uterus.
5.5	9.0	5.0	0.0	0.0	0.5	T	1.0	0.5	Sub-acute bacterial endocarditis.
3.0	8.0	6.0	0.0	0.0	0.0	T	- 1.5	- 1.5	Hydronephrosis. Lobar pneumonia.
1.5	7.5	7.0	0.0	0.0	0.5	- 0.5	- 3.0	- 2.5	Cancer of stomach.
5.0	8.0	4.0	0.5	6.5	6.0	T	4.5	3.0	Dementia præcox, perforation of oesophagus.
7.0	12.0	8.0	T	2.0	1.5	1.5	1.5	T	Bronchopneumonia.
19.0	12.0	3.0	0.0	2.0	10.5*	1.5	1.5	- T	Aleukæmic leucæmia.
3.0 4.0	3.0 3.0	T 0.5	1.0 1.5	1.0 2.0	0.5 1.5	1.0 2.0	1.5 2.5	T T	Aortic aneurism.
4.0	7.0	3.0	0.0	0.0	1.5	1.0	2.0	1.0	Perforation of gastric ulcer.
3.0	10.0	9.0	2.0	0.0	0.0	1.5	3.0	1.5	Pul. tuberculosis.
4.0	12.0	11.0	3.5	4.0	3.5	?	?	?	Mitral stenosis.
2.5	9.0	8.0	0.5	0.0	0.0	T	0.5	T	Chr. pul. emphysema.

notched.

or left ventricular preponderance described in the text.

TABLE III.

*Comparison of methods of sectioning the heart.*

Serial No.	Case No.	LEWIS'S METHOD.				METHOD A.				METHOD B.				First Differ. Vent. Area L/R	Second Differ. Vent. Area L/R
		Vent. Vol.	R	L	S	L/R	Vent. Vol.	R	L	S	L/R	Vent. Vol.	R	L	L/R
2	22	177	31.9	114.6	39.0	3.59	185	37.0	119.3	29.0	3.22	182	44.0	138.0	3.14
4	48	351	74.7	210.5	65.6	2.82	379	90.5	228.3	60.0	2.52	380	121.0	259.0	2.14
6	47	334	77.3	202.4	53.8	2.62	346	84.5	215.2	47.0	2.55	346	105.0	241.0	2.29
7	37	91	21.9	56.4	13.1	2.57	99	26.5	61.0	11.5	2.30	98	32.5	65.5	2.02
10	36	130	32.0	79.3	18.7	2.48	139	38.5	84.3	15.3	2.19	136	42.5	93.0	2.18
17	40	276	74.6	164.8	36.4	2.20	297	91.3	174.5	30.7	1.91	302	108.7	193.1	1.78
18	41	163	45.6	97.5	20.0	2.14	167	51.0	100.0	16.1	1.96	169	58.3	110.5	1.90
19	51	140	39.3	79.6	20.8	2.02	—	—	—	—	—	143	50.3	92.5	1.85
20	52	178	50.8	101.1	26.3	1.99	—	—	—	—	—	184	67.5	116.4	1.73
23	44	138	37.6	73.7	26.7	1.96	142	40.0	77.7	24.0	1.94	143	50.0	93.2	1.85
24	29	323	91.6	177.7	54.1	1.94	339	104.0	193.0	42.2	1.86	335	118.0	217.0	1.84
25	18	372	104.7	202.7	65.0	1.94	385	115.3	213.0	57.0	1.85	390	140.5	240.7	1.76
27	54	119	33.7	64.6	20.8	1.92	—	—	—	—	—	120	43.9	76.9	1.75

28	49	185	58.1	106.5	20.6	1.83	197	69.0	112.7	17.3	1.64	198	75.5	121.7	1.61	0.22	0.03
29	57	107	33.1	60.3	13.3	1.82						111	42.3	68.2	1.61	0.21	—
30	35	152	46.0	82.7	23.3	1.86	160	51.7	87.0	20.8	1.68	161	61.3	100.0	1.64	0.16	0.04
33	46	87	27.0	47.6	12.8	1.75	92	32.5	51.0	8.5	1.60	89	35.7	53.3	1.49	0.26	0.11
35	21	139	43.1	73.5	22.5	1.70	146	48.0	79.0	18.7	1.65	145	60.0	85.0	1.42	0.28	0.23
38	59	160	49.2	83.6	26.9	1.70	—	—	—	—	—	169	69.8	99.2	1.42	0.28	—
39	53	200	63.9	107.8	28.6	1.69	—	—	—	—	—	204	85.8	119.4	1.39	0.30	—
43	42	146	47.9	76.9	20.8	1.61	152	53.7	80.5	18.6	1.50	155	64.0	90.6	1.42	0.19	0.08
44	55	215	71.6	115.4	27.6	1.61	—	—	—	—	—	216	85.6	130.2	1.53	0.08	—
45	38	137	43.7	69.9	23.6	1.60	145	52.5	74.9	18.0	1.43	143	60.0	83.0	1.39	0.21	0.04
49	45	167	58.5	91.4	17.5	1.56	181	68.2	98.0	14.8	1.44	182	76.5	104.5	1.37	0.19	0.07
51	39	186	64.1	96.8	25.3	1.51	197	74.3	103.7	19.0	1.39	195	85.5	110.7	1.30	0.21	0.09
53	50	145	50.4	73.7	20.7	1.46	160	60.0	82.3	17.3	1.37	158	67.0	91.0	1.36	0.10	0.01
56	43	125	45.1	63.3	17.7	1.38	131	50.0	67.7	13.0	1.36	132	56.7	75.0	1.32	0.06	0.04
57	56	208	80.7	96.3	30.7	1.49	—	—	—	—	—	215	104.1	111.2	1.07	0.12	—
58	23	261	107.3	120.2	33.3	1.42	273	117.5	127.7	28.0	1.09	276	132.7	143.7	1.08	0.04	0.01
Averages		187	55.4	103.1	27.8	1.91	205	64.6	115.8	25.1	1.84	196	74.0	121.5	1.68	0.23	0.10

\* L/R (Lewis's method) minus L/R (Method B).

\*\* L/R (Lewis's method) minus L/R (Method A).

TABLE IV. - Average values.

	<i>a</i> Normals. (No cardiovascular disease other than slight atheroma of aorta. No chronic renal or pulmonary disease. No severe anemia. Systolic blood pressure not above 140.)	<i>b</i> Normals. (Same as <i>a</i> , except that 4 cases with distinctly abnormal E.K.G.s are excluded.)	<i>c</i> Normals. (Lewis. Cancer controls.)	<i>d</i> Normals. (Lewis and Gilder.)	<i>e</i> Cases with L/R ratios above 2'20.	<i>f</i> Cases with L/R ratios between 1'80 and 2'20.	<i>g</i> Cases with L/R ratios between 1'50 and 1'80.
No. of Cases .. ..	16	12	11	52	15	16	20
Age .. ..	32.8	31.4	—	—	49.0	48.5	39.9
Height (cms.) .. ..	164.0	165.0	—	—	165.7	159.8	165.5
Weight (kilos.) .. ..	49.7	50.3	49.4	—	47.9	49.3	49.0
Heart weight (gms.) ..	255.0	254.0	304.0	—	419.0	344.0	287.9
Ventricular wt. .. ..	141.0	146.0	148.7	—	230.3	176.0	154.5
R. vent. wt. .. ..	44.2	45.8	44.2	—	51.6	50.2	49.9
L. vent. wt. .. ..	77.0	78.6	81.4	—	139.9	198.9	81.7
Septal wt. .. ..	20.9	21.6	23.1	—	38.5	27.7	22.9
L/R ratio .. ..	1.74	1.73	1.83	—	2.68	1.96	1.64
Vent. wt. .. ..	0.00292	0.00294	0.00301	—	0.00470	0.00363	0.00317
Body wt. .. ..							
Index .. ..	0.25	3.3	—	1.8	5.58	5.34	0.35
P1 .. ..	0.64	0.61	—	0.52	0.49	0.56	0.52
P2 .. ..	1.24	1.20	—	1.16	1.15	1.25	1.34
P3 .. ..	0.66	0.58	—	0.81	0.82	0.69	0.94
Q1 .. ..	0.23	0.22	—	0.51	0.14	0.18	0.24
Q2 .. ..	0.44	0.59	—	0.73	0.35	0.34	0.36
Q3 .. ..	0.75	0.95	—	0.86	0.55	0.38	0.49
R1 .. ..	5.97	5.37	—	5.16	6.96	6.49	5.52
R2 .. ..	8.89	9.52	—	10.32	8.17	7.87	8.62
R3 .. ..	5.34	6.84	—	6.61	4.65	3.68	5.75
S1 .. ..	1.91	2.34	—	2.06	0.58	0.83	1.28
S2 .. ..	2.34	1.46	—	2.23	1.53	1.81	1.30
S3 .. ..	2.03	0.49	—	1.73	3.83	3.39	1.16
T1 .. ..	1.04	1.26	—	1.93	0.04	0.48	0.90
T2 .. ..	1.89	1.68	—	2.46	0.96	0.40	1.39
T3 .. ..	1.12	0.78	—	0.61	1.02	0.11	0.80

*a*. Cases 18, 23, 26, 28, 29, 32, 33, 34, 35, 38, 39, 40, 42, 43, 52 and 53.

*b*. Same as *a*, except that Cases 18, 26, 42 and 52 are omitted.

*c*. See Lewis.<sup>9</sup>

*d*. See Lewis and Gilder.<sup>10</sup>

*e*. Cases 1 to 15 inclusive.

*f*. Cases 16 to 31 inclusive.

*g*. Cases 32 to 52, omitting Case 47.



TABLE IV.—Average values.

<i>h</i>	<i>i</i>	<i>j</i>	<i>k</i>	<i>l</i>	<i>m</i>	<i>n</i>		<i>o</i>	
Cases with L/R ratios below 1.50.	Same as <i>h</i> , but case 54 omitted.	Cases with L/R ratio above 2.50 and vent. wt. ratio above 0.005.	Cases with chr. nephritis and systolic B.P. above 180 mm. Hg.	Cases with chr. nephritis and systolic B.P. below 180 mm. Hg.	Cases of arterio sclerosis.	Aortic regurg. (Lewis.)		Mitral stenosis. (Lewis.)	
7	6	6	8	11	6	13	31	16	40
40.4	—	34.3	44.1	59.2	56.5	—	—	—	—
163.8	—	164.0	163.1	164.0	162.3	—	—	—	—
53.0	—	54.0	53.4	46.0	43.6	66.0	—	53.7	—
360.1	—	560.0	495.3	332.0	302.5	713.0	—	488.0	—
179.6	—	345.0	290.1	153.0	166.6	421.7	—	256.7	—
69.3	—	73.3	65.2	43.3	50.4	112.7	—	97.3	—
86.9	—	211.1	174.2	84.4	92.4	241.7	—	117.0	—
23.3	—	59.9	50.7	25.0	24.0	67.3	—	42.4	—
1.28	—	3.01	2.75	1.99	1.85	2.15	—	1.55	—
0.00344	—	0.00655	0.00539	0.00331	0.00381	—	—	—	—
1.67	-2.42	13.1	9.2	3.04	4.24	—	8.36	—	-10.14
0.56	0.62	0.72	0.59	0.47	0.34	—	1.05	—	1.17
1.63	1.90	1.30	1.30	1.12	1.20	—	1.57	—	2.05
1.46	1.46	0.67	0.94	0.76	1.10	—	0.94	—	1.15
0.54	0.30	0.17	0.20	0.15	0.47	—	0.54	—	0.34
0.64	0.75	0.13	0.47	0.39	0.33	—	0.62	—	0.84
0.61	0.71	0.33	0.62	0.31	0.21	—	0.61	—	1.30
6.21	4.08	10.70	8.90	5.32	5.25	—	9.31	—	3.05
9.29	8.83	8.70	9.00	7.40	7.41	—	11.67	—	11.17
6.07	6.58	3.90	4.70	3.68	3.50	—	5.37	—	11.27
1.11	1.30	0.63	0.60	0.55	0.00	—	1.37	—	3.47
1.43	1.33	2.08	2.06	0.68	0.33	—	3.57	—	2.09
2.44	1.33	6.80	5.56	1.98	2.41	—	5.79	—	1.25
1.30	1.05	-0.65	-0.39	0.65	0.43	—	0.87	—	1.47
1.57	1.58	0.17	0.60	0.87	-0.05	—	1.40	—	2.49
0.44	0.57	0.53	0.91	0.63	-0.03	—	0.65	—	1.16

*h.* Cases 53 to 59.

*i.* Same as *h*, except that Case 54 is omitted.

*j.* Cases 1, 2, 4, 5, 6 and 10.

*k.* Cases 1, 2, 4, 5, 6, 14, 16 and 24.

*l.* Cases 7, 13, 19, 15, 20, 22, 24, 30, 31, 41 and 46.

*m.* Cases 10, 17, 27, 48, 50 and 56.

*n.* See Lewis.<sup>8</sup> The pathological data are from one series of cases, the electrocardiographic data from another.

*o.* See *n*.

TABLE V.—Miscellaneous data.

No.	Case No.	Vent. Wt.	L/R	L-U R	Index.	Carter's Index (degrees).	Inclination of anat. axis (X-ray).	Causes for displacement of heart.
1	58	387	3.83	131.4	33.0**	15	—	
5	3	391	2.72	77.9	14.0* 2.5	16 42	28*	Fibrino-pur. Pericard. Pl. effusion (L).
4	48	351	2.82	76.0	3.5*	53	46*	
11	7	427	2.46	70.4	17.8**	1	36*	
6	47	334	2.62	63.4	16.0*	3	42*	
2	22	177	3.59	57.1	5.5	30	—	Empyema (R).
3	19	224	2.86	51.9	4.0	76	—	
9	33	194	2.50	31.7	9.0	8	43*	
17	40	276	2.20	30.6	7.0*	16	—	Pl. effusion.
8	1	158	2.53	26.6	7.5*	37	—	Aor. aneurism.
12	9	163	2.46	25.5	3.0	68	—	
14	6	181	2.25	22.0	7.0* 3.5	4 71	— —	
10	36	130	2.48	21.6	10.0** 6.5*	11 13	? —	Ascites.
7	37	91	2.57	17.0	2.5	45	?	Ascites.
15	10	146	2.25	17.0	- 3.5	69	—	
18	41	163	2.14	15.5	12.5**	34	—	Ascites.
13	24	101	2.36	14.6	- 6.0	83	—	Ascites, hydrothorax.
25	18	372	1.94	14.2	16.5**	- 39	40*	
16	31	128	2.20	13.4	0.0	60	—	
24	29	323	1.94	12.7	9.5**	- 25	26*	Ascites, hydrothorax.
20	52	178	1.99	9.6	7.5	9	?	
19	51	140	2.02	8.9	4.0	42	47	
21	26	157	1.97	7.3	1.0	55	41	Ascites, hydrothorax.
22	13	160	1.96	7.0	17.0**	- 13	—	Sero-pur. pericard.
23	44	138	1.96	6.0	0.5	59	—	
26	8	119	1.93	4.3	7.0	21	—	
27	54	119	1.92	3.9	5.5	45	—	
28	49	185	1.83	1.9	1.5	55	37	
29	57	107	1.82	0.7	- 13.0*	107	55	Cancer of right lung.

\* X-ray measurements marked with \* were made from teleröntgenograms.

TABLE V.—Miscellaneous data.

C.D. 1.1 plus C.D. 1.3 equals C.D. 1.2 plus or minus.	Vent. Capacity, c.c.		Thickness of Vent. Wall mm.		Interval, days		Remarks.
	L	R	L	R	X-ray to death.	E.C.G. to death.	
11	80	75	16	2	—	1	<i>Q</i> , <i>E.S.</i> interval within normal limits. Leads <i>I</i> and <i>III</i> diphasic. Suggest conduction defect in right branch of His-bundle.
4.5 1.0	—	—	15	5	7	10 8	Change in <i>E.C.G.</i> probably due to change in position of heart following removal of pleural fluid (800 c.c.). <i>M.R.</i> 6.5 cm., <i>M.L.</i> 14.5 cm. (X-ray).
8	45	80	16	4	6	7	Curves anomalous. Inversion of <i>T</i> due to digitalis? <i>M.R.</i> 6.5 cm., <i>M.L.</i> 9.5 cm. (X-ray).
0	—	—	12	2	29	15	<i>M.R.</i> (mid-line to rt. border) 6.5 cm., <i>M.L.</i> 12 cm..
13	65	125	15	3	23	3	<i>M.R.</i> 5.5. <i>M.L.</i> 9.5 (X-ray).
1	18	9	13	6	—	20	Invert. <i>T</i> deflections due to administration of digitalis.
1.5	—	—	10	3	—	38	<i>E.C.G.</i> normal. Ventricular shadow transverse (X-ray report). X-ray plate lost.
2	32	60	12	3	20	20	<i>M.R.</i> 4.5 cm., <i>M.L.</i> 9.5 cm..
6.5	135	115	11	2	—	12	
1	—	—	10	2	—	5	Heart much displaced. Curves anomalous.
6	—	—	11	4	—	0	
8	—	—	11	5	—	20	First curve taken at time of uræmic convulsion.
0.5	—	—	—	—	—	2	
2	20	65	13	2	10	6	Change in form of <i>F.C.G.</i> probably due to removal of ascitic fluid (12½ litres). Heart transverse.
0.5	—	—	—	—	—	3	
0.5	22	44	10	5	55	60	Curves of very low amplitude. Heart displaced. X-ray outline of heart hidden by high diaphragm.
4.5	—	—	9	2	—	8	
2.5	25	75	12	2	—	1	
1	30	48	9	2	—	1	
5	—	—	14	5	5	6	<i>M.R.</i> 7.5 cm., <i>M.L.</i> 11.0 cm. (X-ray).
1	15	50	9	2	—	21	
3	100	110	12	4	6	6	<i>M.R.</i> 6 cm., <i>M.L.</i> 11.5 cm. (X-ray).
2	14	75	18	4	11	0	Heart transverse.
2.5	20	50	12	3	3	0	
2	50	28	8	4	46	4	
2	—	—	12	7	—	1	
0.5	10	40	12	4	—	5	
0.5	—	—	11	3.5	—	30	Curves show slight fling due to high skin resistance.
0	—	—	14	4	—	34	
1	70	100	8	2	1	14	
1.5	30	45	14	5	51	49	Curves within the normal range. Dextrocardiogram precedes leviocardiogram? Vertical heart.

TABLE V.—Miscellaneous data (continued).

No.	Case No.	Vent. Wt.	L/R	L-18 R	Index.	Carter's Index (degrees).	Inclination of antraxys (X ray).	Causes for displacement of heart.
30	35	152	1.80	0.0	8.0	22	35*	
31	11	111	1.80	0.0	6.0	41	35	
33	46	87	1.75	1.0	5.0	42	36	
47	14	18	1.58	-1.3	-4.5	75	—	
32	30	173	1.78	-1.7	-4.0	71	36	Empyema (L). Scoliosis.
34	34	159	1.71	-4.0	0.5	56	—	Ascites.
35	21	139	1.70	-4.1	18.5**	115	—	
36	25	147	1.70	4.5	-6.5	77	49*	Aneurism.
38	59	160	1.70	4.9	-11.0	86	43	
40	4	115	1.67	4.9	2.0	54		
42	28	107	1.65	-5.3	18.0**	0		
41	27	121	1.66	-5.6	-2.5	70		Pl. effusion.
37	32	193	1.70	-5.7	9.0	38		
39	53	200	1.69	-7.2	5.5	40		
45	38	137	1.60	8.7	2.5	73		Empyema (R).
43	42	146	1.61	-9.5	0.0	60		
46	17	157	1.58	-9.5	-1.0	64		
50	12	166	1.56	-10.7	-4.0	81	—	
44	55	215	1.61	-13.6	-3.0	71		
52	60	132	1.51	-13.6	-3.5	70		
52	60	132	1.51	-13.7	6.5	3	45	Pneumothorax.
48	5	184	1.58	-13.8	6.5	39	—	Empyema.
49	45	167	1.56	13.9	1.0	57	40	Ascites, hydrothorax.
53	50	145	1.46	-17.0	0.5	7	—	Pulmonary tuberculosis.
51	39	186	1.51	18.4	-5.0	80	55*	
56	43	125	1.38	18.9	2.5	45	37	Sub-diaphragmatic abscess.
55	2	170	1.42	23.6	2.5	16	25	Aortic aneurism.
					3.5	7		
54	20	199	1.45	26.4	26.5**	7		Tympanites, ascites, hydrothorax.
57	56	208	1.19	-48.7	-8.0	85	46	Chr. pul. Tbc.
59	16	149	0.96	-57.0	-6.0	79	—	Pulmonary emphysema.
58	23	261	1.12	-73.0	-7.0	87	40*	

\* X-ray measurements marked with \* were made from teleröntgenograms.

TABLE V.—Miscellaneous data (continued).

C.D. L1 plus C.D. L3 Vent. Capacity. cubic C.D. L2 position anterior	L	R	Thickness of Vent. Wall mm.		Interval, days		Remarks
			L	R	X-ray to anterior	E.C.G. to anterior	
1	35	85	12	3	40	43	M.L. 4.5. M.L. 8.5 (X-ray).
1	—	—	9	3	44	44	Change in curve due to change in position of heart?
0	80	45	8	1	19	18	
0	—	—	—	—	—	6	X-ray taken in supine position.
0.5	—	—	5	2	—	18	
1	105	75	9	3	0	3	
1	16	24	9	2	—	0	Curves of very low amplitude.
3	25	55	19	3	—	3	Heart normal from clinical and from pathological stand- points. E.C.G. just outside normal range.
1.5	32	54	9	2	12	9	
3	60	115	9	2	—	6	M.R. 4.5. M.L. 7.0 (X-ray).
5.5	—	—	—	—	—	—	Vertical heart.
5.5	—	—	7	2	—	3	
2	10	44	8	2	—	1	
3	65	92	5	3	—	36	
1	40	100	10	3	—	81	
0.5	—	—	—	—	—	38	
2.5	50	150	11	3	—	14	
0	25	90	8	3	—	14	
4	15	85	14	2	—	5	
1	—	—	9	4	—	2	
1	—	—	12	3	—	1	
0.5	30	95	16	5	—	3	
2	19	30	11	4	1	1	
1.5	—	—	9	3	—	12	
1.5	65	75	7	4	6	6	X-ray showed very large heart.
3	30	100	9	2	—	0	
1	30	50	13	4	3	3	Inversion of T due to digitalis.
0	32	75	9	2	40	58	
0.5	—	—	11	4	65.5	3	X-ray plate shows much enlarged transverse heart. Enormous aneurism.
0.5	—	—	—	—	64.7	—	
3.5	—	—	11	4	—	63	
2	12	75	20	8	19	14	
1.5	—	—	10	6	—	73	
3	65	92	10	6	58	1	M.R. 6.0 cm., M.L. 11.5 cm. (X-ray).

TABLE VI.

*Comparison of the electrocardiogram and L-1.8 R value in cases in which the heart was greatly hypertrophied; cases of Lewis and of Cotton included.*

Case.	Ventricular weight.	Index.	L/R	L-1.8 R
1	387	33.0**	3.83	131.4
5	391	14.0** 2.5	2.72	77.9
4	351	3.5*	2.82	76.0
C. 4	421	17.5**	2.55	74.0
11	427	17.8**	2.46	70.4
C. 3	404	29.5**	2.63	70.0
6	324	16.0*	2.62	63.4
L. 1	270.5	19.0**	2.60	52.0
14	276	7.0*	2.20	30.6
L. 2	343	19.0**	2.04	23.0
C. 5	350.5	-10.0	1.97	16.0
25	372	16.5**	1.94	14.2
24	323	9.5**	1.94	12.7
L. 4	308.5	8.0	1.94	12.5
L. 3	416.5	12.5**	1.87	9.0
L. 5	297	4.5*	1.82	2.0
L. 7	292	-7.0	1.60	-19.0
C. 6	333	9.0**	1.30	-24.8
C. 2	201.9	-5.5	1.30	-33.2
L. 6	285	1.5*	1.38	-42.0
58	261	-7.0	1.12	-73.0
C. 1	269	-6.0*	0.82	-116.9
L. 8	287	-15.5**	0.82	-125.0
L. 9	256	-77.0**	0.41	-223.0

C.—Cotton.

L.—Lewis.

TABLE VII.—Effect of respiration on the normal electrocardiogram.

Case No.	P(N)*	P(I)	P(E)	Q(N)	Q(I)	Q(E)	R(N)	R(I)	R(E)	S(N)	S(I)	S(E)	T(N)	T(I)	T(E)
551-L1	0.8	0.6	1.0	0.5	0.0	1.0	11.0	4.5	13.0	1.7	1.0	2.0	3.0	1.7	4.0
551-L2	T	T	T	0.0	0.0	0.0	14.0	15.0	11.0	2.5	3.0	2.5	4.0	4.0	4.0
551-L3	T	T	0.8	0.0	0.0	0.0	4.0	9.5	1.2	2.0	2.0	5.5	1.8	2.5	-0.8 T
Index	..	..	..	..	..	..	7.3	4.0	15.3**	..	..	..	..	..	..
520-L1	T	T	T	0.0	0.0	T	5.0	1.8	7.0	0.0	0.0	0.0	1.0	T	1.1
520-L2	0.7	T	0.7	1.2	1.0	0.8	15.0	17.0	13.0	1.5	2.5	1.2	3.2	2.7	2.7
520-L3	T	T	T	1.0	1.0	0.5	9.0	13.0	6.0	2.0	2.5	2.5	3.0	2.0	2.0
Index	..	..	..	..	..	..	-2.0	-8.7	3.5	..	..	..	..	..	..
527-L1	T	T	0.5	0.0	0.0	0.0	7.0	3.0	9.0	1.5	1.5	1.5	1.5	1.8	2.0
527-L2	2.5	2.2	2.7	0.0	0.0	0.0	13.0	15.0	10.0	0.0	T	1.2	2.0	2.0	2.0
527-L3	1.8	T	1.8	0.0	0.0	0.0	9.0	12.0	T	0.0	0.0	4.0	0.8	0.8	0.5
Index	..	..	..	..	..	..	3.5	10.5	11.4	..	..	..	..	..	..
632-L1	T	T	0.5	0.0	0.0	0.0	2.0	1.0	2.1	2.5	1.0	3.0	0.8	0.5	0.9
632-L2	1.9	1.5	1.7	0.9	0.0	0.4	16.4	13.0	15.0	1.4	2.6	1.7	1.8	0.9	2.3
632-L3	1.1	1.5	0.9	1.1	T	0.9	16.4	12.7	17.3	0.0	1.8	0.0	0.9	0.5	1.1
Index	..	..	..	..	..	..	16.9	-10.9	-18.9*	..	..	..	..	..	..
630-L1	T	T	T	0.0	0.0	0.0	1.5	0.6	2.0	2.2	1.5	3.0	2.0	1.2	3.0
630-L2	1.8	2.2	1.5	2.0	1.7	2.0	17.0	14.5	17.0	0.0	0.0	0.0	7.0	5.0	6.5
630-L3	1.8	2.0	1.2	3.0	2.2	3.0	16.5	15.0	16.0	0.0	0.0	0.0	5.0	4.0	3.0
Index	..	..	..	..	..	..	-17.2	-15.9	-17.0	..	..	..	..	..	..

\* N.—Normal breathing, I. Deep inspiration, E.—Forced expiration, T.—A trace.

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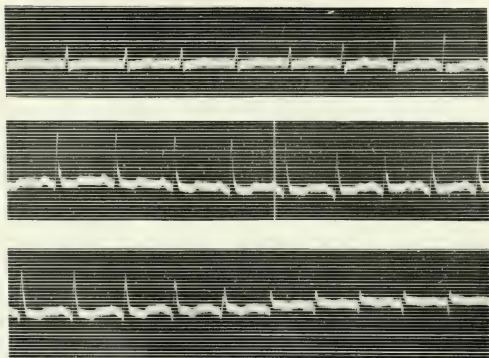


Fig. 2. The effect of forced respiration upon the form of an electrocardiogram which indicated slight left ventricular preponderance. Lead *I* above, lead *II* middle, and lead *III* below. The left end of the figure shows the form of the curve when the breath was held in deep inspiration; the gradual change in the form of the curve was the result of expiration.

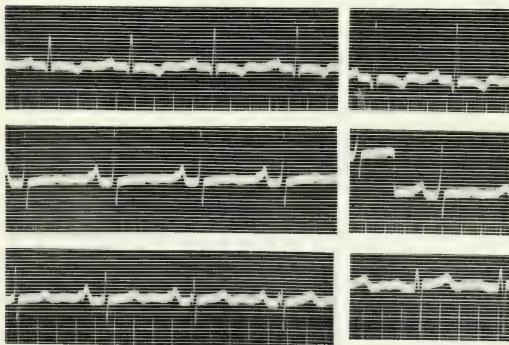


Fig. 3. Similar to Fig. 2. The first part of the curve shows the effect of deep inspiration; the gradual change in the form of the curve was due to expiration. The short curves at the right end of the figure were obtained during quiet normal breathing.



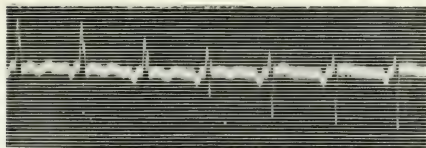


Fig. 4. The effect of forced breathing upon the form of lead III of a curve indicates of left-left ventricular preponderance. Breath held in deep inspiration, then out at curve and slowly expired. Note the appearance of a chest motion as *Q-R-S*, denotes a change in the direction of rotation of the electrical axis.

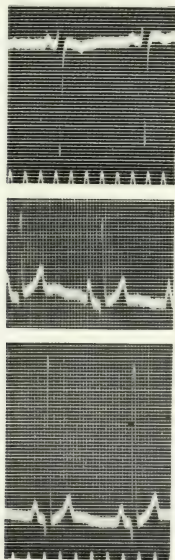


Fig. 5. The electrocardiogram of a case of pulmonary stenosis. Note that leads I and III are not diphasic. Curve taken by Dr. Wellbourne at the Peter Bent Brigham Hospital.



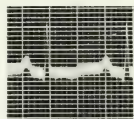
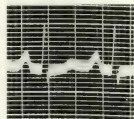
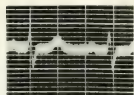


FIG. 6.

FIG. 7.

Fig. 6. A normal electrocardiogram which suggests a transversely placed heart.

Fig. 7. A normal electrocardiogram which suggests that the right ventricle received the excitation wave in advance of the left.

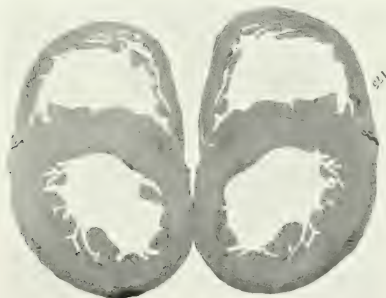


Fig. 9. Photograph of a section of the heart of Case 25. Note line through the septum.



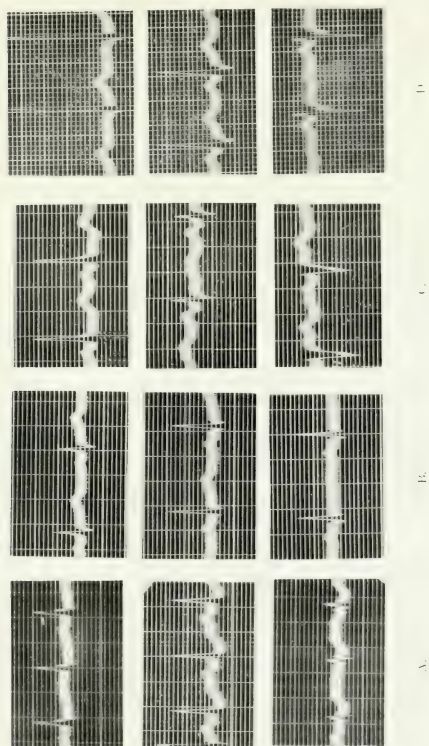
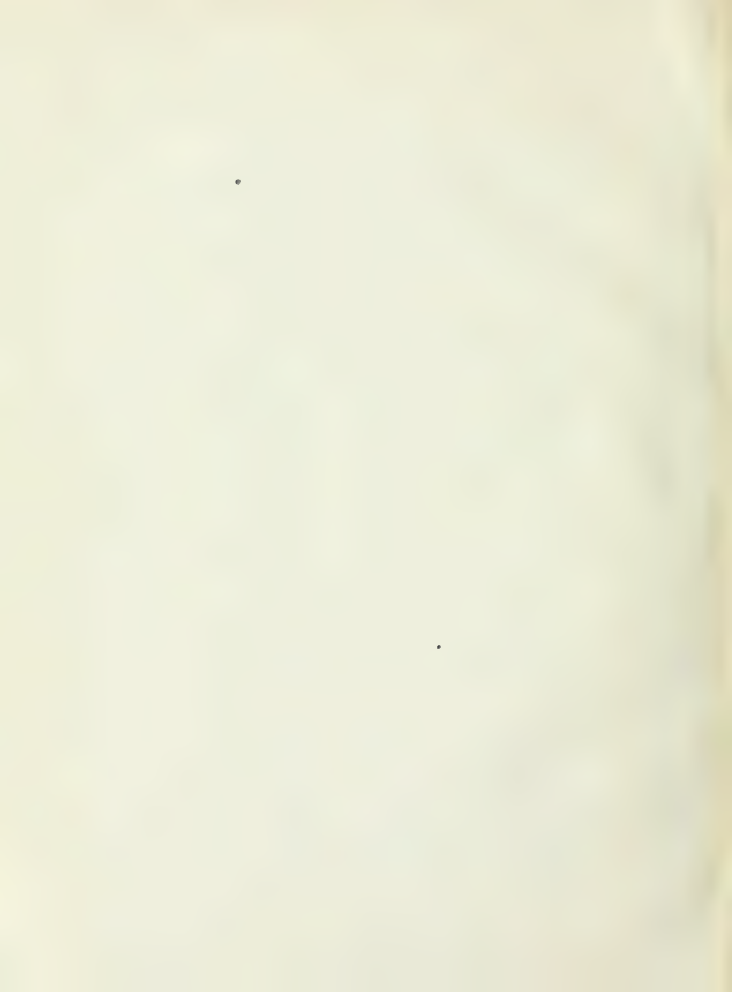


Fig. 8. A, Electrocardiogram of Case 2. B, Electrocardiogram of Case 3. C, Electrocardiogram of Case 12. D, Electrocardiogram of Case 54.





## THE CARDIO-DYNAMICS OF MITRAL INSUFFICIENCY.

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Our current conceptions as to the dynamic consequences of a leaking mitral valve, formulated partly on a priori reasoning, partly on the results of experimental studies, are still at variance. It is pertinent, therefore, to discuss a few of the supposed consequences of mitral regurgitation in the light of data furnished by methods hitherto unemployd in the study of this lesion, and to formulate our conception of the dynamic consequences on the basis of these observations.

### *I.—The dynamics of the left heart and systemic circuit.*

In discussing the normal mechanism of cardiac action, the closure of the mitral valves at the proper time has generally been considered of crucial importance. By virtue of their complete and secure closure in the earliest moments of systole, the ventricle is able to contract isometrically and within 0.04 to 0.05 of a second elevates the pressure to a level exceeding diastolic arterial pressure, thus insuring prompt and rapid expulsion of blood during the succeeding ejection phase.

How is this rapid elevation of pressure accomplished when the mitral valves are incompetent? What, indeed, prevents all the blood from being expelled through the mitral orifice? How can ventricular tension ever be elevated sufficiently to open the semilunar valves? These and similar questions have not been satisfactorily answered.

*Previous work.* In a philosophical consideration of the subject, Schwartz<sup>6</sup> has attempted to give a more precise interpretation of the dynamic alterations concerned and a logical interpretation of the compensatory mechanisms automatically brought into play. Starting with the premises that considerable regurgitation must occur during the isometric contraction phase,\* he argues that one of the first consequences must be a prolongation

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\* Without entering into a discussion as to whether the ventricle contracts isometrically or not when a valvular lesion exists, we shall, for brevity's sake, refer to the entire phase of rising tension before opening of the semilunar valves as the isometric contraction phase.

of this phase. If the duration of systole remains unaltered, the subsequent phase of ejection must be correspondingly reduced. As a result of this, the systolic discharge is decreased and some systolic retention occurs. These two events are held to account for the fall of arterial pressures and the dilatation of the left heart. Schwartz further points out that the only mechanisms which can truly compensate for such a sequence of events are those that operate to abbreviate the isometric contraction phase, lengthened as a result of the lesion. He concludes that four factors operate to accomplish this: (1) The reaction of the ventricles to increased initial tension; (2) the reduced diastolic pressure in the aorta; (3) cardiac hypertrophy; and (4) the beneficial effects of extra-systoles. The first two are especially significant factors for discussion. As regards the second, it is conceivable that if the aortic pressure is reduced, the time required to elevate the ventricular pressure to this lower level will be shorter. The experimental work of Hürthle<sup>4</sup> and Wiggers<sup>11</sup> indicates, however, that this expected relation does not necessarily exist. As regards the first factor, Schwartz quite logically applied the laws demonstrated by Frank in the case of the frog's heart and subsequently shown by one of us to hold in the case of the mammalian heart, viz., that, within limits, the ventricle responds to progressive increases in the initial tension with a steeper rise of pressure during the isometric phase. Schwartz's deductions, however, were not supported by any experimental work of his own.

In 1916, Straub<sup>9</sup> studied the dynamics of acute lesions produced by separating the mitral cusps by means of a tiny wire frame inserted through the auricles. The advantage over previous procedures, which consisted in cutting or hooking back valve segments, lay chiefly in the fact that normal and abnormal conditions could be reproduced many times in succession. His results indicated that during an acute mitral regurgitation there is a marked diastolic and systolic distention of the ventricles, and, to judge from left auricular pressure records, he also believed that an elevation of initial intraventricular tension occurs. Stromhur records indicated that the output of the left heart is only temporarily reduced and then recovers to normal. Volume curves indicated that the tidal volume entering and leaving the left ventricle during a lesion remains unaltered. Aortic pressures were unchanged. These results led this investigator to conclude that many of the essential dynamic mechanisms incorporated in Schwartz's hypothesis apparently do not obtain. Straub believes, however, that the effect of increased initial pressure to abbreviate the isometric phase is of probable importance.

Unfortunately, Straub, in this series of investigations, employed dynamic apparatus which, at other times, he had submitted to severe criticism. Consequently, his work netted only rough results and left unstudied many vital points that can only be determined by the use of optically recording methods.

*Results of our experiments.* In our experimental work, we sought chiefly to interpret the data supplied in optical pressure curves recorded from the left auricle, left ventricle and aorta, but supplemented this by such other experiments as proved necessary. The apparatus, alignment and technic has been described on previous occasions by one of us.<sup>11</sup> For producing the lesion we employed a sound fitted with a plunger as described in detail elsewhere.<sup>10</sup> This was inserted through the ventricular wall into the lumen of the mitral ring. When the plunger was in place the valves closed about the apparatus without leakage and with no appreciable hindrance to the inflow of blood. When the plunger was withdrawn, a definite regurgitation was instantly produced. This could be recognised by the murmur which was always heard on auscultation, and usually felt as a thrill by the hand controlling the plunger. When optical records were taken artificial respiration was temporarily discontinued. Many grades of lesions were thus produced under a variety of circulatory conditions. A total of 20 experiments yielded successful records of pressure curves in the left heart and systemic circuit for analysis. These we believe it more interesting to discuss in a practical rather than quite consecutive order.

*During what phase of the cardiac cycle does the chief regurgitation occur?* There are four phases of the cardiac cycle (Wiggers<sup>11</sup>) during which intra-ventricular pressure exceeds intra-auricular and during which regurgitation might take place. These are (a) the isometric contraction phase (0.05 sec.), (b) the ejection phase (0.11-0.25 sec.), both subdivisions of the period of systole, (c) the protodiastolic phase (0.02 sec.), and (d) the isometric relaxation phase (0.05-0.06 sec.), both early phases of diastole, previous to ventricular filling.

Evidence as to when regurgitation chiefly takes place may be obtained in several ways. We shall, first, analyse the immediate and stabilised changes produced by a lesion in the pressure curves from the left auricle and ventricle. Consistent results were obtained in 13 experiments. The immediate effects are typically illustrated in Fig. 4. The chief phases of the cycle are indicated by lines and letters referred to in the legend. The normal curves are typical, except that, in the left auricular pressure curve, the positive peak during the isometric phase is accentuated, and that, at the beginning of ventricular inflow (*F*), the left auricular pressure falls but little. The former deviation is due to the fact that the heart could not be left to move naturally within the pericardium, which it was necessary to open. The latter deviation is characteristic of left auricular pressure curves when the distention of the left auricle is relatively slight. The moment where the lesion was produced is shown by the star. Note that during the lesion the left auricular pressure is elevated only very slightly during the isometric phase (*B-C*), that in fact it falls quite normally during the latter portion of this phase. During systolic ejection (*C-D*) the auricular pressure rises rapidly, producing a greatly elevated plateau upon which murmur

vibrations characteristic of regurgitation waves are superimposed. This increase in auricular pressure does not end, however, with the onset of diastole (*D*) but continues for about 0.08 of a second into diastole (*D-F*), *i.e.*, throughout the proto-diastolic and isometric relaxation phases. Similar changes are shown in Fig. 5. Such intra-auricular pressure curves give the impression that the regurgitation during the isometric phase is relatively slight, but occurs chiefly during the phase of systolic ejection and during the entire interval of diastole preceding rapid ventricular filling.

These deductions are confirmed by an analysis of intraventricular pressure curves. If any considerable regurgitation occurs during the isometric phase we may anticipate definite changes in the gradient of the pressure curve during this phase. In the majority of cases, however, neither inspection nor the most careful superposition showed any variation whatsoever in the slope of the isometric pressure gradient. Only when the pressure curves were recorded on very rapidly moving paper did some of the curves show a barely recognisable decrease in slope. The pressure at which ejection occurs is obviously lower, and the pressure-maximum (summit) is reduced by virtue of regurgitation during the ejection phase (Figs. 4 and 5).

These findings are so contrary to current clinical conceptions as well as physiological teaching that we deemed it essential to substantiate the results in other ways. This we sought to do by recording the volume changes of the auricles, plethysmographically. Theoretically, this should make it possible to determine, not only the precise moment when regurgitation begins, but the relative volumes regurgitated during the several phases. Practically, however, it is not so easy and at times quite impossible to record volume changes in the auricles with great accuracy. The auricles lying on the base of the ventricles, shift their position with every ventricular movement, and are consequently moved into and out of an auricular cardiometer even with the best adjustment. After considerable experimentation, we have, however, obtained records which, if not quite free from extraneous influences, enable us, nevertheless, to confirm our findings. In the upper record of Fig. 6 are shown *normal* intraventricular pressure changes and corresponding changes in the auricular volumes, as optically recorded by a cardiometer system. We interpret the volumetric changes of the auricular volume curves as follows:—The decrease in auricular volume (*A-B*) is due to auricular systole. *B-C* and *C-D* represent the isometric and ejection phases of the ventricle, respectively. The primary increase and subsequent decrease of auricular volume during these phases are probably accounted for to a considerable extent by movements of the cardiac base. *D-E* represents the combined proto-diastolic and isometric relaxation phases. At *E*, ventricular inflow begins. The records are sufficiently accurate to show the decrease in auricular volume (*E-F*) during the rapid ventricular filling and the subsequent increase in auricular volume (*F-A*) during the phase of diastasis.

In the lower record of Fig. 6 are shown the changes produced by the sudden production of a lesion. When the auricular volume at the end of the isometric contraction phase (*C*) is compared with the normal curves, it is evident that very little additional increase in volume has taken place; in other words, that regurgitation during the isometric phase is very slight. During the systolic ejection phase (*C-D*), the auricular volume increases markedly, and furthermore this increase continues for 0.08 of a second into diastole, *i.e.*, throughout the proto-diastolic and isometric relaxation phases. At the moment that the *a-v* valves open and blood enters the ventricle (*E*), the auricular volume decreases. Incidentally, we note that the inflow volume during the early filling phase (*E-F*) is much greater than normal.

*Are the intervals of isometric contraction and systolic ejection changed?* In a recent communication,<sup>11</sup> one of us pointed out that the duration of these phases can be calculated most satisfactorily from the combined ventricular and aortic pressure curves. We have thus calculated both phases in 15 experiments. A few of these results, as related to previous diastole length, are incorporated in Table I, and a typical immediate effect is shown in Fig. 8. They indicate that sometimes there is a tendency for the isometric phase to lengthen in the first cycle after a lesion. Then the phase returns to normal or becomes slightly shorter. As a rule, it may be said that the intervals do not deviate more than a few thousandths of a second from normal as long as previous diastole remains unaltered and that the isometric contraction phase is never greatly prolonged as Schwartz assumes.

The cause of the slight lengthening of the isometric phase in the first beat following a lesion is undoubtedly occasioned by the small regurgitation into the auricle during this phase, for careful superposition shows a slight decrease in the gradient of pressure development. Under these conditions it takes a longer time to elevate the intraventricular pressure to the level of intra-aortic diastolic. As shown in Fig. 8, however, the diastolic aortic pressure always falls by the time the second beat supervenes. This probably at once counteracts the slight tendency of the phase to lengthen by virtue of the regurgitation and at times acts even to abbreviate this phase. It is doubtful whether this early shortening of the isometric phase is aided by an increasing initial tension or initial length. In most instances, as shown in Fig. 8, the return to normal occurs when initial tension becomes elevated. It was further noted, however, that when the initial pressure subsequently increases (*cf.* Fig. 5) it apparently does not affect the duration of this phase further.

A glance at such figures as are shown in Table I indicates that, with the exception of the beat immediately following the lesion, there is no essential change in the duration of the *ejection phase*. The small variations that occur from beat to beat are no greater than those normally found (*cf.* Wiggers<sup>11</sup>). If any change is detectable it is a slight lengthening of the



TABLE I.—*Durations of systolic phases before and after insufficiency.*

	Beat No.	Previous diastole.	Isometric phase.	Ejection phase.	Total systole.
Experiment C 271, V, C. Lesion .. .. .	10	0.460	0.058	0.140	0.198
	11	0.482	0.058	0.158	0.216
	12	0.505	0.058	0.145	0.213
	13	0.511	0.046	0.142	0.188
	14	0.521	0.048	0.158	0.206
	15	0.521	0.059	0.140	0.199
	16	0.520	0.058	0.138	0.196
	17	0.501	0.057	0.138	0.195
	1	0.403	0.060	0.105	0.165
	2	0.401	0.060	0.108	0.168
	3	0.401	0.057	0.125	0.182
	4	0.527	0.041	0.128	0.169
	5	0.406	0.061	0.113	0.174
	6	0.403	0.060	0.120	0.180
	7	0.403	0.063	0.105	0.168
	8	0.405	0.060	0.121	0.181
	9	0.408	0.062	0.111	0.173
Normal .. .. . (Beat 4, post compensa- tory after premature systole not listed.)	10	0.407	0.065	0.120	0.185
	11	0.408	0.061	0.118	0.179
	12	0.415	0.061	0.111	0.172
	13	0.406	0.064	0.122	0.186
Experiment C 265, II. Normal .. .. .	1	—	0.043	0.165	0.208
	2	0.460	0.050	0.170	0.220
	3	0.462	0.055	0.160	0.215
Lesion .. .. .	4	0.460	0.058	0.165	0.223
	5	0.800	0.039	0.182	0.221
	6	0.479	0.059	0.158	0.217
	7	0.460	0.050	0.160	0.210
	8	0.460	0.060	0.162	0.222
	9	0.465	0.060	0.170	0.230
	10	0.462	0.058	0.163	0.221
	11	0.461	0.058	0.161	0.219
	12	0.465	0.051	0.163	0.214
	13	0.459	0.059	0.164	0.223



average ejection phases which may probably be assigned to a slight increase in the initial tension. Any discussion of such alterations must necessarily be entirely academic and without practical significance.

The establishment of the constancy of the systolic phases is important, not only because this greatly simplifies the discussion of dynamic reactions, but also because they prove that the hypothetical premises upon which Schwartz based so plausible a conception of cardiodynamics in mitral regurgitation do not obtain to any degree in actual regurgitation experiments.

*Changes in the residual and tidal volumes of the left heart and aorta.* Immediately after the induction of a lesion and continuing permanently thereafter, the volume of blood is reduced in the aorta and increased in the left auricle. This is indicated by the fact that the average left auricular pressure increases and the aortic pressure-level falls. It becomes necessary to examine more in detail, however, in what manner the residual volume of blood in the ventricle is affected and also how the tidal volumes change after a lesion.

Whenever the residual volume of the ventricle increases, the ventricle is distended in diastole, and thereby the pressure just previous to systole (*i.e.*, the initial pressure) may be raised. Consequently, if the initial tension (as indicated, *e.g.*, by points *x* in Fig. 8) increases, we may infer that increased diastolic distension has taken place. The possibility exists, however, according to some investigators, that changes in diastolic volume may occur without changes in initial tension. Failure to find increased initial tension may therefore not necessarily be interpreted as indicating that the diastolic volume remains unchanged.

A careful analysis of our experiments shows that, as a rule, the initial pressure is elevated somewhat within a few beats after the lesion has been produced. Thus, out of 18 experiments, the pressure was found to be slightly elevated in 13, unaltered in 3 and reduced in 2. The latter effects appear to be artefacts, however, for such curves show a sharp drop of intraventricular pressure throughout auricular systole. Typical immediate effects are illustrated in Figs. 4 and 8. In the second and third beats, shown in Fig. 8, a slight increase in initial tension is indicated. Such changes are necessarily slight in records obtained by intraventricular pressure manometers and difficult to demonstrate in reproductions of reduced size.

As a rule, the initial pressure continues to mount slightly, so that in records taken 5-15 minutes after the production of the lesion, the initial pressure is still higher (Fig. 5, *x*, last segment). Thus, of 18 experiments examined, this progressive and further increase in the initial pressure was found in 15, but in 3 experiments it became slightly lower again. Obviously these effects hold only when no persistent extra-systoles operate to complicate



the dynamics. The increase in initial pressure occurs whether the heart is beating rapidly or slowly. It was observed whether venous pressures were low or high (*e.g.*, after previous venous infusion). The elevation is more pronounced when arterial resistance is high, *e.g.*, when the aorta was previously compressed, but we have observed it also in cases in which arterial pressures were very low.

These experiments corroborate the observations of Straub, that there is a definite retention of blood in the left ventricle which increases its diastolic volume. It extends his observations by showing that, as in normal hearts, this increase in diastolic volume is accompanied by an elevation of initial intraventricular tension.

A consideration of jointly recorded pressure curves enables us also to discuss the changes in the tidal volume entering and leaving the ventricle. Under stabilised conditions, the volume entering through the mitral valves corresponds in magnitude to the volume expelled through the aortic valves during systole. The tidal volume is then measured by the systolic discharge. During mitral insufficiency, however, the tidal volume represents the sum of the systolic discharge into the aorta and the volume regurgitated into the left auricle. We have already established that, in consequence of a mitral regurgitation, the left auricular pressure increases. Careful analysis of such curves as are shown in Figs. 4, 5 and 6 prove that auricular pressure is not greatly elevated except during the systolic ejection, and early diastolic phases. Consequently, at the moment that the *a-v* valves open (*F* in Fig. 4) a higher filling pressure is available, and, as shown by *E-F* in Fig. 6, this causes a greatly increased inflow of blood into the ventricles. There can be no doubt therefore that the filling volumes are greater.

Is the inflow increased sufficiently, however, so that the systolic discharge is restored to normal? The results obtained by Straub<sup>9</sup> are apparently contradictory. On the one hand, he interprets his ventricular volume curves as showing no increase in tidal volume, and yet, in spite of a leak, the minute-volume recorded by a stromuhr in the aorta appears to return to normal when stabilised conditions have been established. Our own experiments give evidence that, on account of this increased tidal volume, the systolic discharge is restored within a few beats, at least approximately, to normal. Aortic pressure curves, such as shown in Figs. 8 and 9, show that both systolic and diastolic pressures fall for 2 to 4 beats. Then a new dynamic equilibrium is established and both pressures continue for a while at the same lower level. This could readily obtain, provided the tidal volume remained normal and the systolic discharge into the aorta continued to be reduced. In such event, as is readily demonstrated by artificial circulation machines, systolic pressure falls more than diastolic, and the pulse pressure remains smaller as stabilised conditions supervene. In stabilised lesions, however (Figs. 8 and 9), there is always a definite tendency of the pulse pressure to become larger again, and in some instances the normal pulse pressure again returns. This

would tend to show that, in agreement with Straub's stromuhr results, there is at least an approximate restoration of the systolic discharge to normal.

That this *must* occur is also shown by the fact that left auricular pressures continue to increase for only a few beats and then become stationary (Figs. 4 and 5). This can happen only when the systolic discharges of the two ventricles are exactly equal, for, as long as the right ventricle delivers a larger systolic volume through the pulmonary system into the left auricle than the left ventricle can pump into the aorta, the left auricular pressure must continue to increase. The failure of the left auricular pressure to increase after a few beats following the lesion must therefore mean either (1) that, while the systolic discharge of the left ventricle remains reduced, the discharge of the right ventricle is correspondingly diminished, or (2) that the discharges of both ventricles are normal. Anticipating an analysis of our records of right ventricular and pulmonary arterial pressure presented in detail later (cf. page 160), it may be stated that these curves cannot be interpreted as showing that the right ventricular discharge is reduced in the least. We are therefore obliged to explain the dynamic equilibrium in the left auricle as due to a restoration of the normal systolic discharge from the left ventricle.

It is important to clearly understand the compensatory mechanisms whereby the volume of systolic discharge is returned to normal after a lesion. The higher left auricular pressure and greater diastolic inflow supply a larger tidal volume for systolic ejection. The mechanism whereby the left ventricle is able to expel this larger volume is the increased initial tension within the ventricle. By increasing the velocity of pressure development as well as the vigour of its stroke, the larger inflow is actually expelled from the ventricle during systole. Should this mechanism fail, the systolic residues would progressively accumulate, thus rapidly and fatally dilating the ventricles. Further evidence that the increased initial tension is of value in righting the damage done by a mitral leak is given in pressure curves obtained when normal conditions are suddenly restored. If the ventricular pressure curves during insufficiency and immediately after abolishing a lesion are compared, as in Fig. 5, it is obvious that the intraventricular pressure maximum not only returns to, but exceeds, normal for a while. Similarly, systolic and diastolic aortic pressure are higher than before the production of a lesion.

We therefore conclude that the chief compensatory action of a high initial pressure and initial volume consists in the fact that, during a lesion, the increased tidal volume is made use of to restore the systolic discharge approximately to normal. It does not compensate in the sense that the absolute systolic and diastolic pressures are returned to normal, for when the arterio-venous balance has once been upset the arterial system contains less blood and the left auricle and ventricle more.

*II.—The dynamics of the right heart and pulmonary circuit.*

During mitral insufficiency the regurgitated blood elevates the left auricular pressure, especially during the phase of ventricular ejection and early diastole. The "back pressure theory" implies that this increased pressure works backward so that the pressures in the pulmonary artery and right ventricle are also increased and the right heart becomes dilated. On the basis of careful clinical observation, Mackenzie has reached the conclusion that such congestion is not the direct effect of a valve leakage but is referred to and indeed only present when there is a coincident myocardial weakness.

*Previous work.* On the whole, the results of experimental work have not supported the theory that a mitral regurgitation directly causes a damming back of blood into the pulmonary artery and right ventricle. Bettleheim and Kauders,<sup>1</sup> as well as McClure and MacCallum,<sup>5</sup> found no significant variations of pulmonary mean pressure; indeed, the latter investigators often recorded a slight fall. Straub<sup>9</sup> recorded right ventricular and auricular pressures by membrane manometers and found no demonstrable changes in either their initial or maximum pressures.

Several explanations have been offered as to why the natural equilibrium of the pulmonary circuit and right heart are maintained.

(1) The regurgitated blood may be entirely accommodated in the expansible left auricle and its venous tributaries or new intrapulmonary vessels may be opened up. This apparently happens after aortic compression in normal hearts, for Straub<sup>8</sup> found, in such cases, that the volume of the lungs increases without any alteration of pulmonary arterial or right ventricular pressure. According to this conception, which is also favoured by Gerhardt,<sup>2</sup> the increased left auricular pressure will affect neither the pulmonary arterial nor right ventricular pressure and volume until the limit of accommodation has been reached in the left auricle and its venous tributaries. In other words, mitral insufficiency *per se* is able to produce no more than a passive venous congestion.

(2) On the supposition that the reduced systolic discharge of mitral insufficiency causes a smaller volume flow through the peripheral vessels and consequently a diminished venous return, McClure and MacCallum have suggested that the systolic discharge of the right heart is thereby automatically reduced. This would tend to counteract any tendency that back pressure effects may have to elevate the pulmonary arterial pressures.

(3) Henderson and Prince<sup>3</sup> have shown that in the perfused heart a greater distention of the left ventricle acts to push the intraventricular septum to the right and thereby diminishes the capacity and systolic discharge of the right ventricle. Since the left ventricle is thus distended during mitral regurgitation it is possible that the pulmonary balance is maintained in this way.

*Effects on pulmonary systolic and diastolic pressures and on the contour of the pulse.* Optical records of pulmonary arterial pressures are not only more delicate than mean pressure tracings in showing possible effects, but, by changes in the systolic and diastolic pressures, as well as the pulse contour, permit an interpretation of the nature of the compensatory mechanism, if such exists.

In 11 trials pulmonary arterial tracings showed no alterations of either systolic or diastolic pressures. In one experiment systolic pressure declined briefly and then slightly rose. In one experiment only was there a definite but slight increase in systolic pressure. Fig. 9 illustrates the only experiment where the systolic pressure increased slightly. It is obvious that even in this case no considerable volume of blood could have dammed back into the pulmonary arteries.

In cases where no changes in systolic and diastolic pressures were recorded, careful inspection showed, however, that the contour of the systolic summit changes slightly. Thus the systolic plateau which before the lesion was declining, becomes slightly more horizontal after the lesion. In Fig. 9, the cause of the increased systolic pressure rise is clear. It will be noted that following the sharp primary elevation (*a-b*) the pressure mounts more steeply to a summit (*c*) and through this actually elevates systolic pressure a trifle.

Such records enable us to estimate the degree of the "back pressure" effect to a nicety. Apparently only during mid-systole, *i.e.*, when left auricular pressures are elevated to the maximum, is there sufficient *vis-à-fronte* to affect the pulmonary arterial pressure. If the pulmonary pressure curve is declining during systolic ejection, the plateau merely becomes slightly more horizontal during a lesion, but pulmonary systolic pressure is not elevated. If pulmonary pressure ascends during the ejection phase, the slope becomes steeper, and, as a result, systolic pressure is slightly elevated. Since the left auricular pressures are elevated but little during diastole (Figs. 4 and 5) there is no back pressure effect at this time, and consequently diastolic pressures remain unaltered.

The unchanging amplitude of the pulmonary pressure curves also indicates that the systolic discharge of the right ventricle is unaltered. This fails, on the one hand, to support the idea that the pulmonary volumes are kept constant by a reduced discharge of the right ventricle, and, on the other hand, to lend any support to the idea that the right heart helps to compensate for a leakage of the mitral valve by giving a larger discharge. The latter confirms the conclusion reached by Straub,<sup>9</sup> although Stadler<sup>7</sup> believes that when the leak is large the right ventricle compensates. We have been unable to find any support for this assumption, even when valvular insufficiency was very great.

*Are back pressure effects observed in the right ventricle?* We have found it most difficult to obtain synchronous records of right and left ventricular pressures which are at once free from technical errors, and in which the heart is not hypodynamic. The fixation of two ventricles by rigid manometers, together with the introduction of the sound, proved very difficult. Among many failures, we nevertheless obtained several good experiments. Such a curve is shown in the first record of Fig. 10. In this case the right ventricular pressure maximum of the first beat, for some unexplained reason, is slightly higher. Thereafter initial and maximum pressures are unaltered. This was the typical effect. No changes in contour could be detected by most careful study. Obviously such changes in pulmonary arterial resistance as are shown by a change in the contour are not transmitted to the right ventricle. These curves also give no evidence that the systolic discharge is changed in the least. The initial pressure and slope of the pressure curves remained absolutely unchanged. Such effects persist for a considerable length of time after the lesion, and are interpreted as sole effects of the mitral damage.

Owing to the complexity of these experiments the heart was required to work under extremely unfavourable conditions, with the result that it very quickly decreased in vigour. The initial tension in the left ventricle then rose, but this produced only a lower pressure maximum. Obviously the left side dilated, a fact that could readily be verified by observations. In such instances the initial pressure in the right ventricle was also found to be increased, but its pressure maximum was higher. The incipient stages of these changes is well shown in the second record of Fig. 10. Here the left ventricular pressure maximum is just beginning to decrease and the right ventricular pressure maximum to increase. This indicates that in failure of the left heart there is a back pressure effect leading first to a distention of the right ventricle during diastole. As long as the right ventricle is able to respond with greater discharge and higher pressure maximum, however (as in Fig. 10), no systolic retention occurs, and the heart is not decompensated.

### *III.—A conception of the cardiodynamics of mitral insufficiency.*

In formulating our conception of the cardiodynamics of mitral insufficiency, we must begin with an explanation and proof as to why regurgitation occurs to so slight a degree during the phase of rising tension and takes place chiefly during the phase of systolic ejection, and, lastly, why it continues for 0.08-0.09 of a second into the early phases of diastole. Two factors undoubtedly account for this distribution of regurgitation. The isometric contraction phase is of very short duration (0.04-0.05 of a second), and during this interval the pressure increases roughly from 4 to 60 mm. Hg. This short interval is practically required, however, to overcome the inertia of the blood within the ventricles, with the result that, under

the relatively low pressure existing, the blood is not set in backward motion until the aortic valves open. This makes it impossible for any considerable regurgitation to take place, even though an opening of considerable size exists. On the other hand, systolic ejection continues for 0.15-0.25 of a second, and during this interval the intraventricular pressure ranges from 60 to 160 mm. Hg. The continuation of such pressures for many hundredths of a second makes it possible for considerable leakage to take place. Finally, during the early phases of diastole, viz., during the proto-diastolic and isometric relaxation phases, equal to 0.08-0.09 of a second, intraventricular pressure continues definitely above intra-auricular, consequently regurgitation during systolic ejection continues into diastole.

That these physical factors determine the time of regurgitation can be demonstrated successfully by the simple apparatus shown in Fig. 1. It

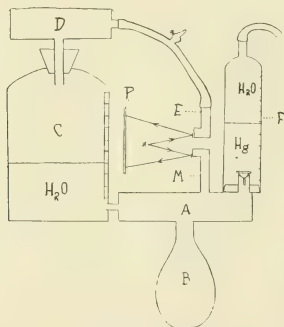


Fig. 1. Physiological apparatus to demonstrate that, under rapid tension development, very little regurgitation occurs for 0.05-0.06 of a second. Description in text.

consists of a chamber (A) to which an optical manometer (M) recording the pressure within it, is attached. The pressure is increased by rapidly compressing a large bulb (B). In so doing, fluid can be displaced either through a tube (1 cm. long and 6 mm. internal diameter) into a bottle (C) against a fluid column varying from 60-150 mm. of water or by a larger tube (1 cm. in diameter) through a valve into a second receptacle (F) containing a mercury column equal to 60-80 mm. Hg. The time relations of regurgitation to the pressure development as well as the volume actually



regurgitated into the bottle (*O*) under different pressure conditions may be optically recorded by connecting the bottle *C* to a segment tambour (*D*) and optical capsule (*E*). We endeavoured in the main to reproduce pressure variations similar to those in the heart.

Fig. 7 shows such records. It is obvious that when, in such a system, the pressure rises rapidly to a point corresponding approximately to the isometric phase (*A-B*), the regurgitation is exceedingly slight. During the subsequent rise and fall of pressure (*B-C'*) corresponding roughly to the ejection phase, a larger volume is regurgitated. As in the heart, this back flow does not cease when compression is stopped (*i.e.*, when artificial diastole begins) but continues for about 0.08 of a second more, *i.e.*, until *D*. The volume curves mount markedly during these phases, not because of any relation to contraction or relaxation of muscle fibres, but solely because the *a-v* pressure-difference is greatest and time is available for this to express itself by an actual transfer of a considerable blood volume from ventricle to auricle. This transfer continues as long as a pressure difference exists between auricle and ventricle, and therefore extends into the early phases of diastole. The fact that the duration of the isometric phase remains practically unaltered is therefore not necessarily associated with any compensatory mechanisms as Schwartz and Straub suggest, but is due solely to the physical fact that practically no energy is lost consequent upon regurgitation. The very slight decrease in rate of tension development that may exist is nicely counterbalanced by a lowered diastolic pressure in the aorta.

The consecutive events that follow appear to be quite clear: (1) By virtue of the mitral regurgitation during the ejection phase of systole, the systolic discharge into the aorta is at once reduced, and in consequence, aortic systolic and diastolic pressures fall. As the height of the ventricular pressure-maximum is governed by the arterial systolic pressure, the former is also decreased. (2) By virtue of the regurgitation, the volume and pressures of the left auricle are increased at the moment that the mitral valves open completely. Under this greater head of pressure the left ventricle receives a greater volume in diastole. This increases the initial pressure and distends the ventricle. Under such conditions the valvularly insufficient, like the normal heart, is capable of expelling a larger tidal volume. While this operates in the valvularly insufficient heart to increase the volume regurgitated to a certain extent, it also has the effect of augmenting the systolic discharge. Therefore, within a few beats after the induction of an insufficiency, stabilised conditions have been restored, left auricular pressure during systolic ejection is not further increased, and the systolic discharge of the left ventricle has been restored approximately to normal, and again equals that of the right ventricle.

The nature of the reaction may be illustrated by hypothetical data shown in Table II.

TABLE II.

	Right vent. discharge.	Tidal volume.	Regurgitation volume.	Systolic ejection.
Normal .. ..	12 c.c.	12 c.c.	0	12 c.c.
After insuff. 1st beat	12 c.c.	12 c.c.	3 c.c.	9 c.c.
2nd beat	12 c.c.	15 c.c.	4 c.c.	11 c.c.
3rd beat	12 c.c.	16 c.c.	4 c.c.	12 c.c.
4th beat	12 c.c.	16 c.c.	4 c.c.	12 c.c.

The augmented volume of blood in the left auricle is accommodated by an expansion of the left auricle and pulmonary veins and possibly by the opening of collapsed vessels. The pressures in the left auricle and pulmonary veins are not appreciably higher throughout the cardiac cycle but augmented only during the phase of systolic ejection. Consequently the *vis-à-fronte* is altered neither during diastole nor the isometric phase of systole. Since the flow of blood from pulmonary arteries to veins thus remains unaltered, the pulmonary diastolic pressures are not affected. If the left auricular pressure becomes very high during systolic ejection, however, the increased *vis-à-fronte* may affect the rate of pressure development during systolic ejection. As the pressure curve usually shows a descending plateau, however, this does not as a rule cause the systolic pressure summit to increase. Only exceptionally, where the ascending plateau rises, does this act to elevate systolic pressure itself. No changes therefore occur in the pressures and volumes of blood contained in the right heart. These changes indicate that the pulmonary arteries may be distended a trifle more during systolic ejection but not during diastole, but they cannot be held to indicate a backing up of blood as conceived of clinically.

#### IV.—Reactions under altered circulatory conditions.

The heart with leaking mitral valves, as the unimpaired heart, is required at times to operate under changed circulatory conditions. Thus the heart rate may change, the arterial resistance be increased or decreased, and the volume of blood returning to the heart may alter. Are the cardiodynamics affected differently than in a normal heart?

1. *Special consequences produced by rate changes.* We have studied the effects of changing heart rate in mitral regurgitation by cutting or stimulating the vagi nerves and find that all the cardiac reactions recently described by one of us<sup>11</sup> are also found when the mitral valves are incompetent. Since the greatest volume of regurgitation occurs chiefly during the ejection phase,



and as the duration of this phase lengthens materially when the heart slows, it may be anticipated that the regurgitation volume increases inversely (though not necessarily proportionally) as the rate.

It is difficult to obtain satisfactory experimental evidence as to the importance of this factor. It has already been pointed out that auricular volume curves are not accurate as regards quantitative studies of the volume regurgitated. Probably, however, the increase in regurgitated volume is fairly proportional to the elevation of left auricular pressure during the ejection and early diastolic phases. Accordingly we can obtain some comparative estimate of the volumes regurgitated by comparing the percentage changes in left auricular pressure during these phases. In order to make comparative studies of the regurgitation at rapid and slow rates, it is necessary to have definite controls. This we attempted to do by recording left auricular pressure in the following sequence :--

1. Normal pressure variations when both vagi nerves had been cut.
2. Curves taken 4-8 minutes after production of a mitral lesion.
3. Curves taken when a continuous vagus slowing was produced during the continuance of the same lesion.
4. Curves taken when the same slowing continued but normal valvular actions had been restored.
5. Curves taken as in 1.

By comparing curves under 1 and 2, the percentage increase in left auricular pressure *during the ejection and early diastolic phases*, can be calculated, and thus a factor for the volume of regurgitation at rapid rates established. By similar comparison of 3 and 4, the percentage change of left auricular pressure during slow rates can be evaluated for similar intervals. Transcribed records of such an experiment are shown in Fig. 2. In these the vertical increase (*x-y*) indicates the actual pressure elevation during systolic ejection. From these the percentage increase is readily calculated. Calculations of several such experiments indicate that the increase in auricular pressure during systolic ejection and early diastole is definitely greater in slow than in rapid beats. Thus in the experiment above referred to, the increase in left auricular diastolic pressure resulting from a mitral leak was 38 per cent. when the cycle length was 0.38 of a second and the ejection phase, 0.115 of a second; whereas it increased to 87 per cent. when the cycle length was 0.64 of a second and the systolic ejection phase was 0.18 of a second. This supplies evidence that the regurgitation is definitely increased in slow beats.

Does this greater regurgitation also imply that the systolic discharge is affected more when the heart is slow than when it is rapid, or is this perhaps compensated by the greater rate of diastolic filling and the greatly increased tidal volume moved during each systole? Our evidence is indirect but very

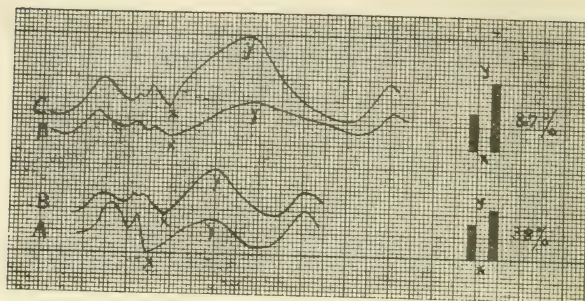


Fig. 2. Four transcribed records of left auricular pressure showing method of determining percentage increase in auricular pressure during systolic ejection. A, normal, rapid heart; B, mitral leak, rapid heart; C, same mitral leak, slow heart; D, normal, slow heart. On margin, actual vertical rises (x-y) blocked in and percentage change indicated.

definite. We have sought to repeat the series of experiments above outlined and note the effect on percentage changes in maximum left ventricular as well as in systolic and diastolic aortic pressures. Such comparisons in four experiments consistently showed that after a lesion there is no greater percentage change in these pressures at slow than rapid rates. This is illustrated by data from two experiments incorporated in Table III.

TABLE III.

*Percentage decrease in pressures.*

	Pressure maximum in vent.	Aortic systolic pressure.	Aortic diastolic pressure.	Average heart cycle.	Average ejection phase.
Experiment C 265 II-III	7	14	17	0.46	0.165-0.17*
	3	13	7	0.95	0.153-0.175†
Experiment C 267 I	8.5	3	6	0.44	0.252-0.26*
	10.0	3	3	0.79	0.241-0.25†
					0.139-0.158*
					0.149-0.159†
					0.18*
					0.208†

\* Variations before lesion.

† Variations after lesion.

It is obvious that even when the ejection phase is lengthened as much as 0.1 of a second there is no greater percentage reduction of aortic and ventricular pressure. Consequently we may infer that the increased regurgitation occasioned by prolongation of systolic ejection is compensated for adequately by the greater tidal volume moved during each systole, with the result that the systolic discharge remains relatively unaltered.

2. *Reaction to changes in venous return.* In mitral insufficiency the heart may under various conditions be required to react to increasing volumes of venous return, either temporary or permanent in character. Among these may be mentioned the physiological increased return during exercise or pathological increases during conditions of hydremic plethora. Is the heart able to prevent pulmonary congestion in such instances by augmenting the systolic discharge? Is the volume of blood regurgitated so increased by virtue of higher intraventricular pressure and by the prolongation of its systole that pulmonary congestion results.

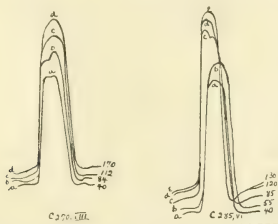


Fig. 3. Two series of transcribed curves of left ventricular pressures during mitral insufficiency showing increasing pressure maxima with increasing initial tension as infusion continues. Numerals indicate right auricular pressure in mm. saline.

Experiments were carried out in which saline infusions were given until the venous pressures equalled from 130 to 220 mm. of saline; for up to these levels normal hearts were able to respond with increased systolic discharge and a progressive elevation of initial tension and pressure maximum (Wiggers and Katz<sup>13</sup>).

In mitral insufficiency experiments, it was found that here, too, the initial and maximal intraventricular pressures increased to the end. Illustrated curves from two experiments are shown as transcribed records in Fig. 3. Owing to the necessary absence of controls it was of course impossible to determine for any given heart whether the *reserve limit* (as judged by the failure of the pressure-maximum to increase with increasing initial tension) was actually as great as normal. It is evident, however, that it is not greatly reduced below that of the average normal heart.

As in normal hearts, we found the duration of systolic ejection increased during augmented venous return. With the prolongation of systolic ejection and a higher pressure-maximum in the ventricle, it may logically be anticipated that the volume of regurgitation would be augmented. That such is the case is indicated by the percentage increase of auricular pressure during the ejection phase when compared with normal conditions. Thus, when these percentage changes were calculated, as previously explained, it was found in an experiment shown in Table IV that under normal conditions of venous pressure the production of a lesion caused about 17 per cent. increase of auricular pressure during systolic ejection. During the course of infusion this percentage pressure-rise became greater and greater, until, when right auricular pressure of 120 mm. had been reached, it equalled 132 per cent. Upon then removing the valvular lesion, the normal pressure elevation was again restored; in fact, the actual systolic rise of auricular pressure was slightly less than at the start.

TABLE IV. (*Experiment C 275.*)

		Venous pressure mm. saline.	Percentage increase or decrease compared with <i>V, b.</i>
Observation V	<i>b</i> Normal .. .. .	40	—
	<i>c</i> During lesion .. .. .	40	17 %
VI	<i>b</i> Lesion and infusion started .. .	55	17 %
	<i>c</i> Infusion continued .. .. .	85	95 %
	<i>d</i> Infusion continued .. .. .	120	132 %
	<i>e</i> Infusion continued .. .. .	130	129 %
	<i>f</i> Restoration to normal .. .. .	130	9 %

Further examination of the auricular pressure curves during such infusion indicates that, while the volume of regurgitation is greater, the auricles are also emptied more completely during each early diastolic inflow phase. This has two effects:—(1) Left auricular pressure is not greatly elevated during diastole; and (2) the systolic discharge is greatly augmented. By virtue of the first factor the resistance in the pulmonary circuit is altered relatively little in diastole, consequently pulmonary diastolic pressure also rises very little (Fig. 11). By virtue of the latter factor both systolic and diastolic pressures increase greatly in the systemic circuit, the pulse pressure becoming greater (Fig. 11). While the increase in pulmonary systolic pressure must, to a large extent, be due to the increased

discharge from the right ventricle, the question arises whether it is not to a certain extent at least occasioned by the elevated left auricular pressure which occurs during systole. That the latter is not an important factor is shown by the fact that if normal mitral action is restored after a generous infusion, pulmonary systolic pressures are not changed in the least. This is well illustrated in the last segment of Fig. 11.

*Reactions to changes in arterial resistance.* Hypertension, whether permanently associated with nephritis, arteriosclerosis, etc., or occurring temporarily as an effect of a sudden physiological strain, more than occasionally complicates mitral regurgitation. Are such conditions accompanied by increased regurgitation and impairment of the heart? May the heart be relieved under such conditions by the use of vasodilating drugs which affect the peripheral vessels?

*Methods and results.* Our experiments consisted in studying the effects produced when arterial resistance was increased through general reflex vasoconstriction or by mechanical compression of the abdominal aorta. The reverse effects of lowered resistance could readily be gauged by the recovery from these procedures, but additional substantiation of the results was obtained by the use of vasodilating drugs such as amyl nitrite and nitroglycerine.

Using the criterion explained in detail above (viz., the percentage increase in left auricular pressure during systolic ejection), we studied the effects of increased arterial resistance on the relative volumes regurgitated. The results of six such experiments indicate without doubt that as the aortic resistance is increased the volume of regurgitation also increases. This occurs to some extent even when comparatively small elevations of aortic pressure occur and when the arterial pressure at the start is comparatively low. The regurgitation becomes very excessive when the elevation of aortic pressure is great, and causes then a general elevation of left auricular pressure at all moments of the cardiac cycle. Conversely, when arterial resistance is diminished, e.g., as a result of aortic decompression or the administration of nitrites, the regurgitation volume lessens.

These conclusions are well illustrated by direct inspection of the decompression curve of Fig. 12, but are even more clearly shown by the data incorporated in Table V.

In observations IV and V, shown in this Table, the effects of moderately increasing the relatively low arterial pressure by stimulation of the right vagus nerve, centrally, are compared in normal hearts and in one with a mitral leak. In valvular leaks (V), the general level of left auricular pressure increased 7 mm. saline and the regurgitation pressure during systole augmented 40 to 50 per cent. Identical changes in arterial pressure produced no alteration of left auricular pressure whatsoever in normal hearts (IV). Similar results follow more marked changes of arterial pressures, as shown

TABLE V.  
*Experiment 315.*

Observation.	Systemic mean pressure. mm. Hg.	Maximum left aur. press. mm. saline.	Actual systolic pressure rise in left auricle. mm. saline.	Percentage increase in systolic press. rise of left auricle. mm. saline.	Remarks.
IV <i>a</i>	66	64	5.5	—	Right vagus (central end). Valves normal.
<i>b</i>	78	64	5.5	0	
<i>c</i>	87	64	5.5	0	
<i>d</i>	81	64	5.5	0	
V <i>a</i>	58	71	10	—	Right vagus (central end). Mitral leak.
<i>b</i>	76	78	14-15	+40-50	
<i>c</i>	75	78	14-15	+40-50	
<i>d</i>	62	77	9-10	0	
VI <i>a</i>	59	74	10-10.5	0	Left vagus (central end). Mitral leak.
<i>b</i>	89	79	15	+50	
<i>c</i>	93	78	14	+40	
<i>d</i>	69	74-75	10.5-11	0	
<i>e</i>	70	74-75	11-12	0	Normal valves.
<i>f</i>	77	76	13-14	+30-+40	
<i>g</i>	87	63.5	5.5	-45	
VII <i>a</i>	69	65	6	—	Left vagus (central end). Normal valves.
<i>b</i>	105	65	6.6-5	0	
<i>c</i>	105	64	6	0	
<i>d</i>	75	64	5	0	
VIII <i>a</i>	84	72	10-10.5	—	Aortic compression. Mitral leak.
<i>b</i>	138	80	15	+50	
<i>c</i>	177	103 ?*	30 ?*	+200*	
<i>d</i>	182	110	42	+320	
<i>e</i>	90	94	20	+100	
<i>f</i>	63	54	8	-20	
IX <i>a</i>	78	74	15	+20	Aortic compression normal (very slight regurgitation).
<i>b</i>	153	86	18	+20-+33	
<i>c</i>	178	96	18-20	-20	
<i>d</i>	105	80	12	-33	
<i>e</i>	63	60	10	—	

\* Curves off drum; estimated changes.

in observations VI and VII. In observations VIII and IX are shown the effects produced when extreme changes in arterial pressure are produced as a result of aortic compression. In observation IX the curves show a very slight inherent leakage, however, so that the differences, though marked, are not as great as shown in cases where absolutely normal reactions followed. The results show that whereas during a lesion (VIII) the systolic volume regurgitated brings an estimated percentage increase of auricular pressure of over 300, when aortic pressure rises from 84 to 182 mm. Hg, with only a slight leakage, the increase is not more than 33 per cent. when arterial pressure is raised from 78 to 178 mm. Hg by aortic compression.



This great augmentation of left auricular pressure also raises pulmonary systolic and diastolic pressures. The initial and maximum pressures in the right ventricle are also elevated. Furthermore, the right auricular pressure is found to increase so that it is quite readily detected by crude measurements with a saline manometer. There can be no doubt, therefore, that increased aortic resistance dams back blood not only into the left auricle and pulmonary veins, but also into the pulmonary arteries and chambers of the right heart.

We may be reminded at this juncture that similar effects have been reported to occur when the mitral valves are intact. A recent review of this literature,<sup>12</sup> as well as personal experiments, indicates that while this does occur in some animals, it is absent in others, the factors determining the incidence of "back pressure" effects not being as yet fully understood. Under these conditions, we could not profitably pursue an ultimate inquiry as to whether the back pressure effect found in our experiments was actually greater than if the mitral valves had been intact. Since, however, left auricular pressure was relatively little affected by increased aortic resistance in these experiments (cf. Table V) when the valves were normal, whereas it did increase markedly when the valves were insufficient, it appears that, in our experiments at least, the back pressure effects were distinctly due to the valvular lesion.

Does the increased regurgitation reduce the systolic discharge when stabilised conditions obtain? Since the aortic pulse pressure may have been reduced as a natural consequence of the increased peripheral resistance, it does not help to decide this question. Left ventricular pressure curves show, however, a sustained increase in both initial and maximum pressure. This, together with the fact that left auricular pressure returns promptly to normal levels on decompression (Fig. 12), shows that the left ventricle is able to react as a normal heart to increased strain for considerable intervals of time. It may also be noted that the stabilisation of left auricular pressure further indicates that the left and right ventricles eject equal volumes of blood. As there is no evidence of a reduction of right ventricular ejection, we may assume that the left ventricle is able, even with leaking valves, to eject normal quantities into the aorta.

### *Summary.*

1. When the mitral valves are rendered insufficient in an experimental way the following dynamic changes occur:—

- a. Owing to the short interval of isometric tension increase, and also to the fact that intraventricular tension ranges from a few mm. to only 60 mm. of Hg, very little regurgitation into the left auricle occurs during this phase of systole.

- b. The chief backflow occurs during the phase of systolic ejection and during an interval extending approximately 0.08 to 0.09 of a second into diastole, for during these intervals intraventricular pressure is very high.
- c. By virtue of this regurgitation, systolic discharge of the left ventricle is at once reduced, and in consequence both systolic and diastolic pressures fall, pulse pressure decreasing.
- d. Since left auricular pressure increases chiefly during the phase of systolic ejection up to the time when the *a-v* valves open, the filling pressure for the left ventricle becomes greater and consequently the tidal volume entering the left ventricle augments. This operates consecutively (1) to distend the left ventricle, (2) to increase the initial tension, and (3) to restore the systolic discharge to normal. In this way the balance of the circulation is restored within a few beats, in the sense that the systolic discharge of the right and left ventricles become equal again and left auricular pressure does not rise further. It does not compensate in the sense that aortic and left auricular pressures are restored to normal, for once the arterio-venous balance has been upset, the arterial system contains less blood and the left auricle more. If aortic pressures fully recover (which was not the case in our experiments) the peripheral vasomotor apparatus is involved.
- e. As long as the cardiac muscle is efficient, the increased volume of blood contained in the left auricle during systolic ejection is accommodated by an expansion of the left auricle and its venous tributaries. Consequently no "back pressure" effects are produced in the pulmonary artery or right heart.
- f. The very slight regurgitation during the isometric phase in some experiments causes the gradient of the intraventricular pressure curve to become slightly more gradual. Owing to the counterbalancing effect of a lowered diastolic pressure, the isometric phase is not lengthened thereby; indeed, owing to the subsequent elevation of initial tension, this phase usually is slightly shorter than normal. These changes are so slight, however, as to be of theoretical interest only.

2. Under altered circulatory conditions, special variations of the following nature were observed :—

- a. During cardiac slowing, the phase of systolic ejection is prolonged and a larger volume of blood regurgitates into the left auricle. This only temporarily decreases the systolic



discharge, for it is compensated quickly by an elevation of filling pressure and consequently an increased tidal volume.

- b* When the venous return to the right heart is augmented experimentally, the left ventricle responds with increasingly greater initial and maximum pressures as well as larger systolic discharge up to the levels equal to the average normal heart. The reserve power, if reduced, is undoubtedly still very considerable.
- c* When arterial resistance is increased in the systemic circuit, the regurgitation volume increases markedly at once, thereby elevating not only left auricular pressure but causing also a damming back of blood into the pulmonary artery and right heart. During this progress systolic discharge is decreased until initial intraventricular tension has been considerably elevated. When this obtains, the systolic discharges of the two ventricles are again equal and a new stable equilibrium is restored.

3. As regards the alignment of our conclusions with those of other investigators the following brief comparisons may be added :—

- a* The hypothesis of Schwartz, that during mitral insufficiency the isometric phase lengthens until it is neutralised by a decreased diastolic pressure and an elevation of initial pressure, is theoretically correct. The prolongation is so very slight, however, and compensation occurs automatically within so few beats after a lesion, that this factor cannot be regarded as of practical significance in discussing the altered dynamics. Schwartz's conclusion that considerable regurgitation occurs during the isometric phase is not substantiated; on the contrary, the amount is quite negligible.
- b* The conclusions of Straub, that a marked ventricular distention and an elevation of left ventricular and auricular tension occurs, are confirmed. The contention, based on studies of volume curves, that the tidal volumes entering and leaving the ventricles during stabilised conditions are unaltered, is not corroborated; in fact, our results indicate that it is precisely by virtue of such a larger tidal volume that the systolic discharge is restored to normal.
- c* Mackenzie's conception that "back pressure effects" are not directly caused by valvular lesions, a conception also confirmed by experiments of Bettelheim and Kauders, McClure and MacCallum, is substantiated. Our results indicate, however,

that this is not prevented by a compensatory decreased discharge of the right heart, either as a result of a decreased return, suggested by McClure and MacCallum, or by a crowding of the intraventricular septum to the right, as indicated in experiments of Henderson and Prince. It occurs, we believe, with undiminished discharge of the right ventricle, because, as Gerhardt suggested, the excessive volume of blood is accommodated by an expansion of the left auricle and its tributaries.

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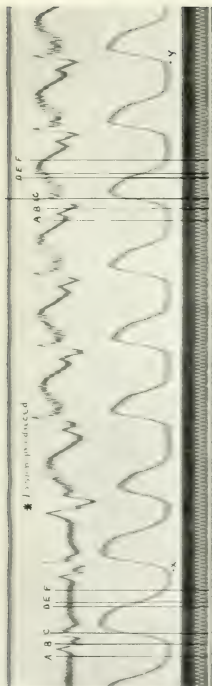


Fig. 4. Pressure curves in left auricle (upper) and left ventricle (lower). Time 0.02 of a second. *A B*, auricular systole; *B C*, isometric contraction phase; *D E*, protodiastolic phase; *E F*, isometric relaxation phase; *F A*, early diastole in flow phase. Points *x y* show slight elevation of initial pressure. Further description in text.

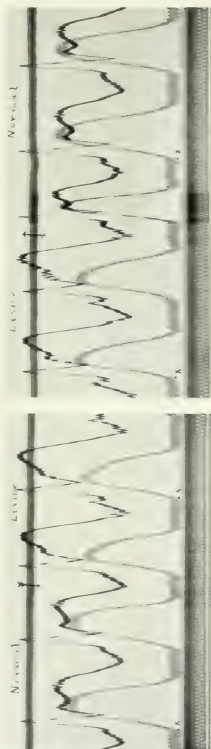


Fig. 5. Two segments of a record showing left auricular (upper) and left ventricular (lower) pressures. In first segment is shown the effects produced in first two beats after a lesion. In the second segment are shown the effects produced 10 minutes after incidence of a lesion and return to normal. Arrows indicate where lesions were produced and normal conditions restored. Points *x* indicate initial pressures at different times.



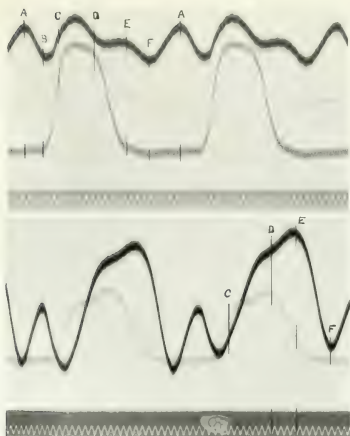


Fig. 6. Two segments showing annular volume curves (dark curve) and intraventricular pressure curves (lighter curve). Upper segment shows normal curves; lower segment, during mitral regurgitation. *C*, beginning of systolic ejection. *D*, end of systole. *E*, beginning of diastolic inflow. Further description in text.

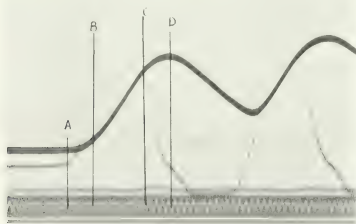


Fig. 7. Pressure and regurgitation curves obtained with apparatus shown in Fig. 1. Note especially relatively slight regurgitation (heavy curve) during "isometric phase" (*A-B*) even when this is over 0.08 of a second, and continuance of regurgitation during early diastole (*C-D*). *A*, beginning of compression. *C*, end of compression.



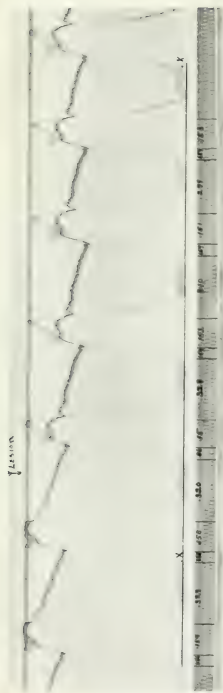


Fig. 8. Records of intra-arterial and left intra-ventricular pressures, before and immediately after a lesion. Numerals on time record indicate durations of isometric contraction, systolic ejection and total diastole in each cycle. *c*, points for comparing initial pressures.

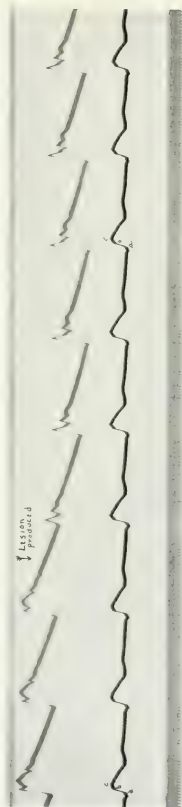


Fig. 9. Pressure curves in aorta (upper) and pulmonary artery (lower) showing temporary reduction of pulse pressure in aorta with return to normal amplitude and also persistent lowering of both systolic and diastolic pressures. Pulmonary systolic pressures only a shade higher; diastolic pressure unaffected (as indicated by comparison with penial line). Other letters referred to in text.





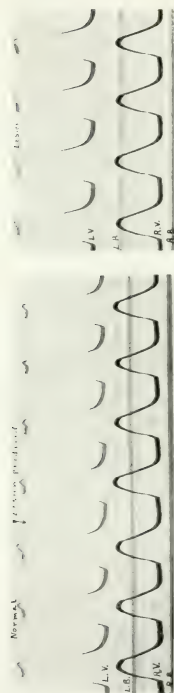


Fig 10. First record shows immediate effects of a mitral lesion on pressures in left and right ventricles. Second record, effects 15 minutes after a lesion. *L.V.*, left ventricular pressure; *L.P.*, base line for same; *R.V.*, right ventricular pressure; *R.P.*, base line for same.





Fig. 11. Four segments of records showing effects of venous infusion on systolic and diastolic pressures in aorta (upper) and in pulmonary artery (lower). In last segment effect of restoring normal initial function shown by arrow. *A.P.*, aortic pressure; *P.A.*, aortic pressure; *P.P.*, pulmonary artery pressure; *P.B.*, pulmonary base line. Arrows pressures resulting in right auricles in four segments as follows: (1) 62; (2) 74; (3) 92; (4) 220 mm. saline.

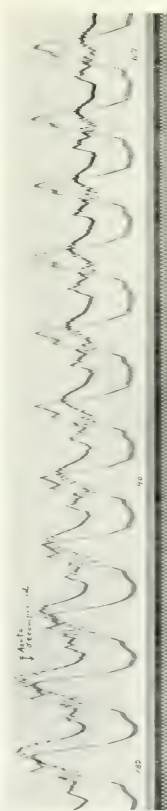


Fig. 12. Curves of left ventricular (lower) and left auricular pressures showing immediate effects which a reduction of arterial resistance has on the systolic regurgitation into the auricle. Figures for mean arterial pressures as calculated from supplementary drum record marked directly on record.



# THE INFLUENCE OF CIRCULATORY DISTURBANCES ON THE GASEOUS EXCHANGE OF THE BLOOD.

## I. THE OXYGEN SATURATION OF THE ARTERIAL BLOOD IN TACHYCARDIA.

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THE occurrence of cyanosis in association with tachycardia is a relatively common event. This is particularly the case in auricular fibrillation, auricular flutter and paroxysmal tachycardia, where dilatation of the heart has supervened. The cyanosis, when it does occur, may be due to several causes. In the first place it might be a manifestation of deficient oxygenation of the arterial blood consequent on the tachycardia or irregular action. It might possibly be brought about through some respiratory lesion interfering with the proper aeration of the pulmonary blood, such as congestion or oedema of the lungs. On the other hand, the cyanosis might be a purely capillary phenomenon resulting from a greatly diminished circulation rate whereby the blood in the capillaries is rapidly depleted of oxygen giving rise to an actual tissue want of oxygen. The factors which might produce such a slowing of the circulation rate are not at present fully understood.

Harrop<sup>2</sup> has investigated the oxygen saturation of the arterial blood of a number of cases of auricular fibrillation. He found a considerable desaturation in certain of these cases. There was not, however, a direct relationship between the oxygen desaturation and the increase of the heart rate, nor was the improvement in the anoxæmia coincident with any pronounced or conspicuous change in the heart rate. It is evident that in many of the cases there was considerable respiratory mischief, but to what degree this was present there is not sufficient data given to determine. Harrop also estimated the carbon dioxide content of the arterial blood, which he found to be uniformly below normal, but it was not constantly related to the depreciation of the oxygen saturation. If the arterial oxygen

desaturations were due to pulmonary complications, it might be considered that the carbon dioxide would be retained in the arterial blood through the same cause. This, for several reasons, might not necessarily be so. The anoxæmia would render the respiratory centre more sensitive to the normal  $p_{H_2}$  of the blood, and in consequence hyperpnoea would result in order that the carbon dioxide of the arterial blood might be kept at the new threshold. This would be further accentuated if there should be any slowing of the circulation rate. If the pulmonary complications were in the nature of an œdema, this would not necessarily be uniformly distributed throughout the lungs, and in consequence the hyperpnoea would wash out carbon dioxide from the functioning alveoli in sufficient amount to compensate for the

TABLE I.

*Oxygen saturation of the arterial blood in cases of arricular fibrillation.*

Case No.	Heart rate.	Oxygen per cent. saturation, of 100 c.c. of arterial blood.	Signs of œdema of lungs.	
1	75	91	+	
2	120	91	+	
3	80	96	—	
	78	92		
	78	90	+	
	78	97	+	Oxygen given.
4	90	95		
5	130	75	+++	Delirious.
	126	96	+++	Oxygen given 4 litres per minute. Pe- lirium disappeared.

relatively nonfunctionating portions. Furthermore, the retention of carbon dioxide in the blood of the œdematous portions of the lungs would not be of the same order as the interference with the transference of oxygen on account of the greater solubility and increased diffusion pressure of carbon dioxide, and also the character of its dissociation curve. It is therefore possible that an important cause of anoxæmia, in certain cardiac cases, may be coincident congestion, or œdema of the lungs.

Barcroft<sup>1</sup> and his co-workers have investigated a case of paroxysmal tachycardia. They found that there was no decrease in the oxygen saturation of the arterial blood; in fact, this was distinctly increased. They also found that there was a great decrease in the circulation rate.

In Table I the arterial blood oxygen saturation in five cases of auricular fibrillation is detailed. It will be noted that the degree of oxygen desaturation is in no degree proportionate to the increase of the heart rate. On the other hand, there is a rough parallelism between the degree of anoxæmia and the œdema of the lungs. This is further emphasised by the effect of increasing the partial pressure of oxygen in the inspired air. It was considered probable that if the anoxæmia were due to œdema of the lungs, that by increasing the partial pressure of oxygen in the alveoli the greater diffusion force thus exerted would overcome the mechanical difficulties offered by the œdema fluid. It was not thought that the increase of the partial pressure of oxygen in the relatively normal alveoli would materially influence the oxygen saturation of the mixed arterial blood, as the blood leaving these alveoli would be almost normally saturated (95 per cent.), and would be only slightly increased beyond this (99 per cent.), but it was expected that the blood passing through the œdematous portions of the lungs would be materially enriched with oxygen and thus conspicuously change the oxygen saturation of the mixed arterial blood. The results obtained in cases 3 and 5 (Table I) fully substantiated this expectation.

In order to observe the effects of tachycardia, without pulmonary complications, upon the oxygen of the arterial blood, the following experiments were performed. Dogs were used under paraldehyde anaesthesia, (a small amount of ether being employed during the operative procedure to ensure full anaesthesia) with artificial respiration. The sternum was bisected, and the divided portions drawn aside, exposing the pericardium, which was opened from the superior vena cava to the ventricular apex and the cut margins stitched to the chest wall. The heart was thus amply exposed for a Cushing myocardiograph to be attached to the ventricular muscle. Great care was taken that the artificial respiration was not excessive, but at the same time that it was sufficient fully to ventilate the lungs. On account of the possible increase above normal of the pulmonary ventilation it was not justifiable to draw any conclusions from the carbon dioxide content of the arterial blood. Therefore these estimations were omitted. The oxygen saturation of the arterial blood from the carotid artery was estimated by the Haldane new blood gas apparatus<sup>2</sup>. The different types of tachycardia were produced by electrical stimulation of the auricle. A rapid irregular rhythm producing a ventricular response, similar to that found in a severe degree of auricular fibrillation, was induced by a faradic current being passed through electrodes placed upon the auricle. A regular tachycardia was induced by a galvanic current interrupted to produce 230 effective shocks per minute.

Examples of the results obtained in a number of experiments are set forth in Table II. In experiment 10 some difficulty was experienced in properly adjusting the pulmonary ventilation. As a consequence, a certain degree of anoxæmia was present during the normal cardiac rhythm. This,

TABLE II.

*Oxygen saturation of arterial blood in experimental tachycardia.*

Expt. No.	Cardiac rhythm.	Cardiac rate.	Oxygen per cent. saturation of 100 c.c. of arterial blood.	Time.	Remarks.
10	Normal rhythm	102	87		
	Irregular rhythm	206+	80		
	" "	210+	90		
	Normal rhythm	112	89		
11	Normal rhythm	90	98	4.00 p.m.	
	Irregular rhythm	230+	100	4.12 "	
	Vent. fibrillation	-	99.7	4.18 "	Blood from left ventricle.
12	Normal rhythm	86	90	2.50 p.m.	
	Irregular rhythm	198+	99	3.10 "	
	" "	204+	96	3.28 "	
	" "	200+	99	3.50 "	
	Normal rhythm	98	96	4.14 "	
14	Normal rhythm	110	100	3.10 p.m.	
	" "	90	99	3.20 "	
	" "	86	97	3.50 "	
	Regular tachycardia	230	98	4.09 "	
	" "	230	92	4.18 "	
	Normal rhythm	100	99	4.40 "	
	Irregular tachycardia	206+	97	5.12 "	

NOTE. The samples were taken 15-20 minutes after the end of the tachycardia in each instance.

however, did not show any consistent increase during the period of tachycardia. In the other experiments little difficulty was experienced in maintaining the oxygen saturation to a normal degree during the period of normal cardiac rhythm.

It will be noted in all the experiments recorded that the oxygen saturation of the arterial blood does not conspicuously deviate from normal.



Any change that does occur is usually in the direction of an increased oxygen saturation. This substantiates the findings of Barcroft.<sup>1</sup>

It may be concluded, therefore, that tachycardia, whether regular or irregular, does not in itself produce a decrease in the oxygen saturation of the arterial blood, but that, if such tachycardia induces failure of the circulation and pulmonary congestion or œdema, such a decrease of oxygen saturation will follow.

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# THE INFLUENCE OF CIRCULATORY DISTURBANCES ON THE GASEOUS EXCHANGE IN THE BLOOD.

## II. A METHOD OF ESTIMATING THE CIRCULATION RATE IN MAN.

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MANY problems relating to the gaseous exchange in the blood would appear to be in some manner influenced by the circulation rate, hence it has become increasingly important to devise a reliable means of estimating this in patients suffering from cardiac disease. Haldane and his co-workers,<sup>1</sup> and Henderson,<sup>2</sup> have developed methods which have given consistent results for normal persons who understand the method when it is applied to themselves. The principle of both these methods is to determine the mixed venous and mixed arterial blood carbon dioxide tensions, and knowing the volume of carbon dioxide per minute exhaled, to calculate the circulation rate from these data. But these methods are not necessarily applicable to patients\* who are suffering from varying degrees of respiratory distress. We have, therefore, attempted to perfect a method which would be applicable to abnormal as well as to normal individuals.

The method of Douglas and Haldane<sup>2</sup> is carried out by making up in a Douglas bag about 50-75 litres of a gas mixture, having, approximately, the carbon dioxide tension expected in the venous blood (*i.e.*, about 5-6 per cent. of carbon dioxide). The subject then exhales deeply, inhales from the bag, exhales into the air, then inhales from the bag. This is repeated three times in a period of 12-15 seconds, and the last exhalation is made into a rubber tube similar to that used for collection of alveolar air by the Haldane and Priestley<sup>3</sup> method. This exhalation is interrupted when 1,500 c.c. of air have been expired. A sample of the expired air at this stage is then rapidly taken, and the expiration is continued until a total of 3,000 c.c. have been expired, when a second sample is taken. If these two samples give an identical value, this is taken as indicative of the venous carbon dioxide tension. This is corroborated by the procedure being repeated with a gaseous mixture containing between 8-9 per cent. of carbon dioxide. It would be expected that, as this mixture is breathed, the excessive carbon

dioxide would be taken up by the blood, and eventually it would come into equilibrium with the venous carbon dioxide tension. These two processes are repeated with percentages of carbon dioxide, which gradually approach each other until stable readings are obtained, and these indicate the average carbon dioxide tension of the venous blood. We have attempted to apply this procedure to normal non-skilled subjects, and to patients, and have found it very difficult.

The method of Henderson and Prince<sup>2</sup> was developed from the Higgins-Plesch method of determining the alveolar air. They found that after a certain number of isolated rebreathings from a bag that the carbon dioxide tension remained fairly level for a short period. They took this observation to indicate the venous carbon dioxide tension if the procedure had not lasted long enough to allow the arterial blood so exposed to return as venous blood. They, therefore, adopted the plan of making the subject forcibly exhale, then take a deep breath out of and into a bag containing a carbon dioxide mixture approaching that of alveolar air. By repeating this procedure at intervals they found that the carbon dioxide tension in the bag became steady (usually after 6 rebreathings-), which they took to indicate the venous carbon dioxide tension. This time employed in the rebreathing might be a rapid inspiration and expiration, holding the breath in the interval, the whole time occupied being 10-15 seconds, or a slow inspiration of 5 seconds, and a slow expiration of a like duration.

We have attempted to employ this method upon normal persons and patients with indifferent results. The resultant tensions of the carbon dioxide varied considerably. We came to the conclusion, after many observations, that there was difficulty in getting a proper mixture of the gases in the lungs after one inspiration, unless the breath were held for a longer period than corresponds to the return of the arterial blood as venous. As this period of time is variable, it was difficult in patients to choose a safe interval.

In view of these difficulties, we have adopted the principles of the preceding methods, but have modified them in the following manner so as to overcome the difficulties associated with the examination of pathological subjects.

It is important that the patient should be subjected to as simple a routine as possible. A bag of about five-litre capacity is almost filled with expired air, containing about 5 per cent. of carbon dioxide. The subject exhales as deeply as possible, then takes a deep inhalation from the bag, expires into the bag deeply, inspires a second time,\* and finally expires forcibly into the bag. In the tube leading from the mouthpiece to the bag there are side tubes which may be directly attached to a gas analysis apparatus or to a Haldane gas-sampling tube. In this manner, a specimen of the last of the expired air may be obtained. The object of the rebreathing is to

\*It is important that this respiratory effort should be continued, even though the bag be empty or the lungs completely inflated, until the final expiration is done.

promote a certain degree of mixing between the residual air in the lungs after the first forced expiration and the air inhaled from the bag. The time factor is not, therefore, so important, provided the whole procedure does not take longer than 15 seconds when at rest, and 5 to 10 seconds during exercise. In patients who have difficulty in making a forced expiration this single rebreathing is of great importance as it helps greatly to bring about a rapid mixture of the air in the lungs and in the bag. The procedure, as described, is repeated at short intervals until the carbon dioxide tension of the expired air becomes constant. This usually requires 4 to 6 repetitions when reaching the venous carbon dioxide tension from below upwards. In order to confirm this finding, 250 to 300 c.c. of carbon dioxide are added to the air in the bag and the rebreathing repeated. (A

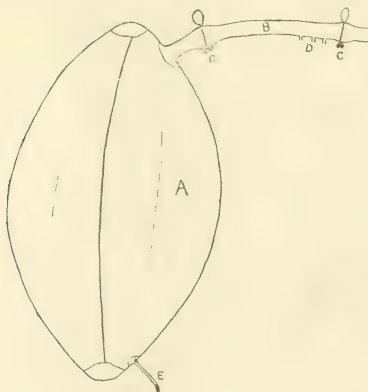


Fig. 1.

- A. Large sized bladder of about 5 litres capacity.
- B. Hose tubing, 30 cms. long, 2 cms. diameter.
- C.C. Large strong spring clips.
- D. Holes for insertion of ends of Haldane gas sampling tubes
- E. Tube for introducing carbon dioxide. End closed by means of small piece of glass rod.

small amount of oxygen may also be added.) Each successive analysis shows a diminution of the carbon dioxide percentage until a constant is obtained which agrees with the first procedure. This stage usually necessitates 5 to 7 rebreathings.

The bag used by us with its various attachments is shown in Fig. 1. It consists of a large-sized rubber bladder with small and large inlet tubes. The smaller inlet serves for the introduction of additional carbon dioxide, or other gas, and is closed by means, either of a spring clip, or a small piece of glass rod. The larger opening is made by a piece of rubber tubing, about 30 cms. long, and 2 cms. diameter, the walls being thick enough not to kink readily, but not so thick as to prevent the lumen from being occluded by means of the spring clips. In this tube, about 10 cms. from the mouthpiece, and about 3 cms. apart, are placed three side openings in which may be inserted the ends of evacuated Haldane gas-sampling tubes, or the end of the burette of the Haldane gas analysis apparatus. In the latter case those not in use are closed by means of small pieces of glass rod. When the bag has been filled with expired air and the side tubes either closed by means of glass rods or gas-sampling tubes, the spring clip nearest the bladder is permanently released, while the one nearest the mouthpiece is pressed by the subject when breathing out of and into the bag.

The arterial carbon dioxide tension is estimated from the alveolar air by the Haldane-Priestley method.<sup>5</sup> If consistent results be not so obtainable it is directly estimated by examining the blood by arterial puncture. The alveolar air determinations have sufficed in the present observations, but our experience shows that the arterial estimations are by far the most satisfactory in patients.

The total carbon dioxide exhaled during a definite period of time is determined by the Douglas bag method. This expired air is usually collected for five minutes after a preliminary period to ensure that the subject is comfortable, and not inconvenienced by the mask, etc. The expired air is collected under conditions identical with those of the previous steps. The pulse rate is taken frequently during the whole observation in order that an average may be obtained to estimate the output of the heart per beat. This frequent counting is most important in subjects who are being examined during exercise.

Having obtained the venous and arterial carbon dioxide tensions, it remains to transpose these into volumes per cent. of carbon dioxide, as represented by the dissociation curve. The dissociation curve of Christiansen, Haldane and Douglas<sup>4</sup> is practically a straight line between 30 and 60 mm. pressure of carbon dioxide. It might be expected that any variation above or below the curve between these points would give a parallel curve, and thus the difference between the venous and arterial volumes per cent. of carbon dioxide would remain the same. Liljestrand and Lindhard<sup>6</sup> have claimed, however, that the dissociation curves in different individuals vary not only in level, but also in shape, confirming the observations of Hasselbalch.<sup>1</sup> This would require, therefore, that the curve be determined for each individual over the interval between the venous and arterial carbon dioxide tensions. Whether this variation in shape of the curve be sufficient in normal

people' to introduce a serious error is not, at present, definitely settled. We have evidence to lead us to be quite confident, however, that the shape of the curve may vary in pathological conditions. It is necessary, therefore, to determine the curve separately for each patient before the percentage volume of carbon dioxide in the venous and arterial blood may be estimated.

In the following protocols a number of examples are given illustrating the method of procedure and the means whereby the circulation rate is calculated.

# PROTOCOL I.

25/10/21 Subject, H.W.D. Barometer, 761.

Successive number of intermittent rebreatings.	CO <sub>2</sub> %	CO <sub>2</sub> pressure mm.	Pulse.	Remarks.
3	6.33	45.2		
4	6.61	47.2	78	
5	6.76	48.3		
6	6.75	48.2	66	
				300 c.c. CO <sub>2</sub> added to bag.
11	7.04	50.1	72	
12	6.82	48.7		
13	6.83	48.8	74	

Average of 5, 6, 12 and 13, 6.79% of CO<sub>2</sub> = 48.5 mm. CO<sub>2</sub> pressure in mixed venous blood.

Alveolar air contains 5.60% CO<sub>2</sub> = 40 mm. CO<sub>2</sub> pressure.

∴ mixed venous blood contains 54.7 vols. per cent of CO<sub>2</sub>.

mixed arterial " " 51.2 " " "

Difference " " 3.5 " " "

Expired air 7.15 litres per minute, and contains 3.93% of CO<sub>2</sub>. Ther., 20°C. Bar., 761.  
∴ factor for reduction to dry volume at standard temperature and pressure 0.912.

Hence CO<sub>2</sub> output per minute =  $\frac{7150 \times 0.912 \times 3.9}{100} = 254$  c.c.

∴ blood flow per minute =  $\frac{254}{3.5} \times 100$  c.c. = 7.27 litres.

Average pulse rate, 72.5. ∴ output per beat,  $\frac{7270}{72.5} = 100$  c.c.

\* From CO<sub>2</sub> dissociation curve.

N.B. — The expired air was collected during an accurately timed five-minute period, and a correction was made for the 0.03% of CO<sub>2</sub> normally present in atmospheric air.

## PROTOCOL II.

25.10.21. Subject, L. J. M. Barometer, 762.

Successive number of intermittent rebreathings.	CO <sub>2</sub> %	CO <sub>2</sub> pressure mm.	Pulse.	Remarks.
5	7.00	50.1	56	300 c.c. CO <sub>2</sub> added to bag.
6	6.79	48.5		
7	6.73	48.1	56	
8	6.90	49.3		
11	7.31	52.3	58	
12	6.85	49.1	56	

Average of 5, 6, 7, 8 and 12 = 6.85% of CO<sub>2</sub> = 49.1 mm. CO<sub>2</sub> pressure in mixed venous blood.Normal alveolar air = 5.80% of CO<sub>2</sub> = 41.4 mm. CO<sub>2</sub> pressure.∴ mixed venous blood contains 55.2 vols. per cent. of CO<sub>2</sub>.

mixed arterial " " 51.7 " " "

Difference " " 3.5

Expired air 9.14 litres per minute, containing 3.01% of CO<sub>2</sub>. Ther., 20°C. Bar., 762.  
∴ factor, 0.913.Hence CO<sub>2</sub> output per minute =  $9140 \times 0.913 \times \frac{2.98}{100} = 249$  c.c.∴ blood flow per minute =  $\frac{294 \times 100}{3.5} = 8.40$  litres.Average pulse rate, 56. ∴ output per beat,  $\frac{8400}{56} = 150$  c.c.

## PROTOCOL III.

27.10.21. Subject, W. M. W. Barometer, 761.

Successive number of intermittent rebreathings.	CO <sub>2</sub> %	CO <sub>2</sub> pressure mm.	Pulse.	Remarks.
5	6.52	46.6	61	300 c.c. CO <sub>2</sub> added to bag.
6	6.52	46.6		
10	6.83	48.8		
11	6.69	47.8	59	
12	6.51	46.5	60	

Average of 5, 6 and 12 = CO<sub>2</sub> 6.52% = 46.5 mm. CO<sub>2</sub> pressure in mixed venous blood.Normal alveolar air = 5.63% of CO<sub>2</sub> = 40.2 mm. CO<sub>2</sub> pressure.∴ mixed venous blood contains 54.0 vols. per cent. of CO<sub>2</sub>.

mixed arterial " " 51.1 " " "

Difference " " 2.9

Expired air 37.7 litres in five minutes, containing 3.35% of CO<sub>2</sub>. Ther., 18.3°C. Bar., 761.  
∴ factor, 0.920.Hence CO<sub>2</sub> output per minute,  $\frac{37.7}{5} \times 0.920 \times \frac{3.32}{100} = 230$  c.c.∴ blood flow per minute =  $\frac{230 \times 100}{2.9} = 7.93$  litres.Average pulse rate, 60. ∴ output per beat,  $\frac{7930}{60} = 132$  c.c.



## PROTOCOL IV.

27/10/21. *Subject, J. C. M. Barometer, 761.*

Successive number of intermittent rebreathings.	CO <sub>2</sub> %	CO <sub>2</sub> pressure mm.	Pulse.	Remarks.
3	6.19	44.2	60	300 c.c. CO <sub>2</sub> added.
4	6.20	44.3		
5	6.22	44.4		
7	7.82	55.8	66	
9	6.64	47.4		
10	6.28	44.8	66	
11	6.22	44.4		

Average of 3, 4, 5, 10, 11 = CO<sub>2</sub> 6.22% = 44.4 mm. CO<sub>2</sub> pressure in mixed venous blood.Normal alveolar air = 5.40% CO<sub>2</sub> = 38.5 mm. CO<sub>2</sub> pressure.∴ mixed venous blood contains 53.4 vols. per cent. of CO<sub>2</sub>.

mixed arterial " " 50.3 " " "

Difference ∴  $\frac{2.8}{100}$  " " "Expired air 302 litres in five minutes, containing 3.86% CO<sub>2</sub>. Ther., 18°C. Bar., 761.  
∴ factor 0.92.Hence CO<sub>2</sub> output per minute,  $\frac{3080}{5} \times 0.92 \times \frac{3.86}{100} = 217$  c.c.∴ blood flow per minute,  $\frac{217 \times 100}{2.8} = 77.5$  litres.Average pulse rate, 64. ∴ output per beat, 121 c.c.

## PROTOCOL V.

28.11.21. *Subject, J. C. M. During exercise on Martin bicycle ergometer. Barometer, 760.*

Successive number of intermittent rebreathings.	CO <sub>2</sub> %	CO <sub>2</sub> pressure mm.	Pulse.	Remarks.
3	7.48	53.3	141	200 c.c. CO <sub>2</sub> added.
4	7.82	55.8		
5	7.89	56.3		
6	8.91	63.5		
7	8.19	58.5		
8	7.82	55.8		

Average 4, 5, 8 CO<sub>2</sub> 7.84% = 55.9 mm. CO<sub>2</sub> pressure in mixed venous blood.Normal alveolar air = 5.80% CO<sub>2</sub> = 41.4 mm. CO<sub>2</sub> pressure.∴ mixed venous blood contains 58.1 vols. per cent. of CO<sub>2</sub>.

mixed arterial " " 51.7 " " "

Difference ∴  $\frac{6.4}{100}$ Expired air 81 litres in three minutes, containing 4.50% of CO<sub>2</sub>. Ther., 18.6°C. Bar., 760.  
∴ factor, 0.917.Hence CO<sub>2</sub> output per minute,  $\frac{8100}{3} \times 0.917 \times \frac{4.47}{100} = 1104$  c.c.∴ blood flow per minute,  $\frac{1104}{6.4} \times 100 = 17.25$  litres.Average pulse rate, 141. ∴ output per beat, 122 c.c.

## PROTOCOL VI.

4.11.21. Subject, W. J. F. Barometer, 742.

Successive number of intermittent rebreathings.	CO <sub>2</sub> %	CO <sub>2</sub> pressure mm.	Pulse.	Remarks.
2	6.28	43.6	78	
3	6.41	44.5		
4	6.46	44.9		
5	7.50	52.4		250 c.c. CO <sub>2</sub> added to bag.
9	6.51	45.2		
10	6.37	44.3		
11	6.46	44.9		
12	6.46	44.9		
13	6.55	45.5		

Average of 3, 4, 9, 10, 11, 12, 13 CO<sub>2</sub> 6.46% = 44.9 mm. CO<sub>2</sub> pressure in mixed venous blood.Normal alveolar air 5.55% of CO<sub>2</sub> = 38.7 mm. CO<sub>2</sub> pressure.∴ mixed venous blood contains 53.3 vols. per cent. of CO<sub>2</sub>.

mixed arterial " " 50.3 " " "

Difference ∴ 3.0

Expired air 36.1 litres in five minutes, containing 3.50% of CO<sub>2</sub>. Ther., 18°C. Bar., 742.  
∴ factor, 0.897.Hence CO<sub>2</sub> output per minute =  $\frac{36.1}{5} \times 0.897 \times \frac{3.47}{100} = 22.5$  c.c.∴ blood flow per minute =  $\frac{22.5}{3} \times 100 = 7.50$  litres.Average pulse-rate, 78. ∴ output per beat,  $\frac{7.500}{78} = 96$  c.c.

It is noteworthy that in Protocols IV and V the output per beat showed an extremely close agreement. This is in accordance with the finding of Douglas and Haldane, that, during exercise, the increased blood flow is obtained mainly by increase of heart rate, and not by increase of the output per beat.

In conclusion, we wish to express our indebtedness to Drs. Fetter and Walwyn for acting as subjects, and to Mr. I. J. Macdonald for assistance in some of the experiments.

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# VENTRICULAR TACHYCARDIA AS THE RESULT OF THE ADMINISTRATION OF DIGITALIS.

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It is well known that sudden death may occur in the course of treatment with digitalis or allied drugs. From experimental pharmacology we know that when animals are poisoned heavily with digitalis the initial changes are followed by at first coupled action and later by a very rapid and irregular heart action: a *delirium cordis* sets in and death intervenes. (Cushny,<sup>1</sup> Meyer and Gottlieb,<sup>2</sup> Poulsen<sup>3</sup>).

It is probable that in man the same stages occur. It has been proved electrocardiographically<sup>2</sup> that digitalis coupling is the result of ventricular extrasystoles.

In the following cases I have had the opportunity of recording by the electrocardiograph an irregular rhythm, which developed while patients were under treatment with digitalis.

*Case I.*—A 50-year old married woman was treated at the hospital from August the 10th to October the 7th, 1921, and again from October the 26th, until she died on November the 3rd. She had never had rheumatic fever; she knew of no venereal infection. There had never been any pregnancy. Her health had been perfect except during the last year, when she has complained of shortness of breath and of a feeling of constriction of the chest in walking, especially in ascending stairs. The last eight days, before the first admittance, she grew worse, and was treated with digitalis by her doctor.

On admission, she was found to be a well nourished woman, rather short of breath, the respiration being 32. The temperature was normal; the pulse was 96 regular. A systolic as well as a diastolic murmur was heard over the whole precordial area; the murmur was audible in the big vessels. By X-ray, a general dilatation was found. There was a distinct capillary pulse, and the pulse in the radial was of the waterhammer kind. Crepitations were heard at the bases of the lungs. The liver extended 2 cm. below the costal margin. There was no patellar reflex, and the Wassermann test was positive. The systolic blood pressure was 170, the diastolic 75.

Digisolvin\* was administered in a dose of 15 drops three times daily, and was continued for six days. (This amounts in all to 1.6 grammes of *folia digitalis titrata*.)

After six days' stay in hospital antisyphilitic treatment was commenced (inunction with unguent. hydrarg. and intravenous injections of neosalvarsan): 30 inunctions and 2 grammes of neosalvarsan were given in all. During this treatment she improved slightly, and was able to walk about in the grounds of the hospital. The urine was scanty and at times contained a trace of albumen.

In the intervals between the stays in hospital she grew steadily worse: she was compelled to stay in bed, developing increasing oedema of the ankles and the lower limbs.

The examination of the heart on October the 26th showed the signs unchanged. Digisolvin was again administered (20 drops three times daily). The pulse-rate was about 100 for the first five days, the rhythm being regular. On the sixth day, the pulse, in the morning, was 160, and very irregular: she complained of palpitations and some giddiness. There was no vomiting, but some nausea was felt. In the forenoon the pulse was found to be 120, and showed pronounced coupling: for this reason digisolvin was discontinued (she had taken in all 300 drops, corresponding to 1.8 grammes of *folia digitalis titrata*). An electrocardiogram was obtained (Fig. 1).

On the following days the pulse-rate was about 120, and when examined, the rhythm of the heart was regular, but she was too weak to be brought to the electrocardiograph. Death occurred 2½ days after the attack of tachycardia.

At the post-mortem, syphilitic aortitis and an aortic aneurism were both found. Both ventricles were hypertrophied, and there were signs of universal stasis. There was no thrombosis in the coronary arteries.

*Case II.*—A 61-year old washerwoman was admitted to the hospital, October the 27th, 1921, and died on November the 15th. Many years before admission she had rheumatic fever: afterwards she enjoyed good health, but for the last 2-3 years, when palpitation and shortness of breath in walking were felt. Off and on, there was some oedema of the ankles. Last summer she was three months in hospital for her cardiac ailment, and during the stay here she developed pneumonia. During October she grew gradually worse and developed a considerable oedema of the lower limbs and of the abdominal wall.

On admission, the heart was considerably enlarged; a systolic as well as a diastolic murmur was heard at the apex. The action was tumultuous, about 160, at the same time the radial pulse-rate was only 114. The liver

\* Digisolvin is a physiologically standardised Danish preparation of digitalis: 25 drops correspond to 0.15 gramme of *folia digitalis titrata*.

extended 3 cm. below the costal margin. There was some cyanosis and the respirations were 44. The urine was scanty and contained traces of albumen.

She was treated with digisolvin (25 drops three times daily) and diuretin, but grew gradually worse. Repeated examinations of the heart showed no change in the signs except on November the 10th, when the action was found to be quite regular and the rate about 180 per minute; the heart-sounds were now almost fetal. The liver now extended 5 cm. below the costal margin, and there was tenderness in the hypochondrium. There had not been any slowing of the pulse or coupling before this tachycardia occurred, nor had she complained of nausea.

The total amount of digisolvin given in the 13 days before the tachycardia was 975 drops, corresponding to 4.85 grammes of folia digitalis titrata.

The following day the action was again quite irregular.

*Electrocardiograms* were taken October the 29th, November the 10th and 11th. The electrocardiograms of October the 29th and November the 11th showed auricular fibrillation, with the signs usually ascribed to right-sided preponderance (Fig. 2). Electrocardiograms on November the 10th (Fig. 3) show a peculiar phenomenon, which is described at a later stage.

At the post-mortem an old endocarditis of the mitral valves was found; hypertrophy of the right ventricle and hypertrophy with dilatation of the right auricle. There was no thrombosis in the coronary arteries.

#### *Further observations and discussion.*

In both these cases a tachycardia occurred suddenly; in the one the rate was about 160, and the rhythm was irregular; in the other the rate was about 180 per minute, and the rhythm was regular.

In *Case I* the tachycardia, which occurred in an attack two and-a-half days before death, is illustrated by the electrocardiogram (Fig. 1). A few normal complexes are seen with their preceding *P*-waves; between them are several abnormal deflections caused by ventricular extrasystoles generated in different foci. In parts of this curve two or three of these abnormal complexes follow each other directly without the interposition of normal beats. The *P*-waves are seen throughout the whole lead, although they are buried in the abnormal ventricular complexes. In the parts of this curve, where every sequential beat alternates with a ventricular extrasystole, the rate is 120 per minute; in the parts where the ventricular extrasystoles follow directly upon each other the rate corresponds to about 180 per minute. Over the whole curve the rate is about 133 per minute.

To sum up, this and other electrocardiograms show that, during the period when the pulse rate was 120 and coupled, a condition of bigeminal

action, resulting from regularly occurring extrasystoles, was present. When the rate was higher, 173, 160, etc., the extrasystoles were more frequent, occurring in groups.

With regard to *Case I I*, the most conspicuous facts are the following :—

A patient presenting auricular fibrillation and the signs of right-sided preponed-ance (Fig. 2) was under treatment with digitalis without any apparent effect at all. There had been no preliminary symptoms of over-dosage, such as slowing of the pulse, coupled beats or nausea. Suddenly she developed an attack of tachycardia, the rate being 186 per minute, and the rhythm regular. The electrocardiogram now showed a remarkable form of tachycardia (Fig. 3). Being regular it could not have been caused by impulses from the auricles, which were still fibrillating, but must have resulted from a new rhythm arising in the ventricle.

In all three leads (Fig. 3) it is seen that the ventricular complexes alternate: a complex in which the most prominent deflection is directed upwards is constantly followed by one in which the most prominent deflection is directed downwards.

A very similar curve has been published by Lewis and Levy.<sup>7</sup> In their experiment on cats, with low tensions of chloroform vapour, they produced an irregular tachycardia caused by ventricular extrasystoles supposedly generated in multiple foci. From time to time they obtained electrocardiograms similar to Fig. 3, and they explained them as being composed of premature contractions alternately generated in separate foci. In giving small intravenous injections of adrenaline chloride to cats under the influence of low tension of chloroform vapour, these irregularities ultimately passed into that of ventricular fibrillation.

The day after Fig. 3 was obtained, the tachycardia had disappeared and the electrocardiogram was similar to that of Fig. 2.

As shown experimentally<sup>8</sup>, and in a recent paper clinically by Robinson and Hermann<sup>12</sup>, thrombosis of the coronary arteries may be followed by a tachycardia of ventricular origin: this tachycardia is often preceded or followed by ventricular extrasystoles<sup>7</sup>. In neither of my two patients was thrombosis of the coronary arteries found at the post mortem: this cause can therefore be excluded.

It has been shown that the administration of low tension of chloroform vapour in cats is constantly followed by ventricular extrasystoles from multiple foci, giving rise to ventricular tachycardia, this being a precursor of ventricular fibrillation (7 and 8). These irregularities have been supposed to result from the chloroform vapour (in low tension) producing an exaggerated irritability of the ventricular muscle.

Comparing the curves from my patients with the chloroform curves we find that they are very similar. In the first of my patients coupling is found alternating with extrasystoles generated in separate foci: in the second a ventricular tachycardia is found giving the same curious electrocardiogram as those of Lewis and Levy (their Fig. 6).

We know that digitalis is prone to produce ventricular extrasystoles in certain subjects (4 and 9). Robinson and Bredeck<sup>12</sup> have published a case in which the intravenous injection of strophanthine produced numerous ventricular extra-systoles arising from separate foci: the first part of their Fig. 7 is very similar to my Fig. 3. Cushing<sup>1</sup> believes that the explanation of the fast and irregular action of the heart in animals poisoned with digitalis is to be found in the increasing irritability of the cardiac muscle.

For these reasons it seems probable *that the administration of digitalis in my two patients directly caused the attacks of the ventricular tachycardia, and that these are to be ascribed to an irritable condition of the ventricle, produced by the drug.*

It is now an obvious conclusion that the direct cause for sudden death under the administration of digitalis may lie in this hyperirritability. That sudden death may occur in patients showing ventricular extrasystoles is known, and the possibility of ventricular fibrillation as the cause of death has been discussed.<sup>5, 6</sup> A very irregular and rapid heart-beat is regarded as a transitional stage leading up to ventricular fibrillation<sup>7</sup>: this transitional stage is termed by Levy<sup>8</sup> "potential fibrillation."

#### Resumé.

Two cases under treatment with digitalis suddenly developed a ventricular tachycardia without previous warning and died a few days later. The possibility of this being due to hyperirritability of the ventricles arising out of the administration of digitalis, and the possibility of sudden death under treatment with digitalis being caused by ventricular fibrillation, is discussed.

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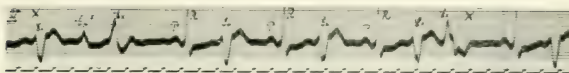


Fig. 1. Lead II. A few sequential beats *R* are seen with their preceding *P* waves. The remaining complexes *R* are due to ventricular extrasystoles coming from different foci. These complexes are not seen by the initial *P* waves. The wave *P* (about 10) corresponds to a *P* wave combined with a ventricular extrasystole. The curves are standardised, but not leads II and III in Fig. 3. The timesmarker always signifies 1/10 of a second.

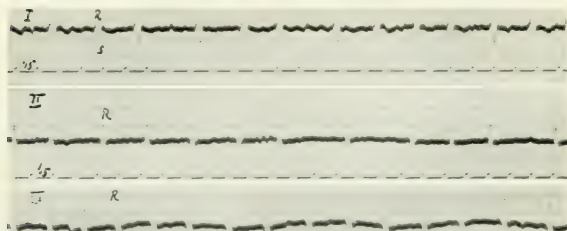


Fig. 2. Atrial fibrillation with regularised preponderance.

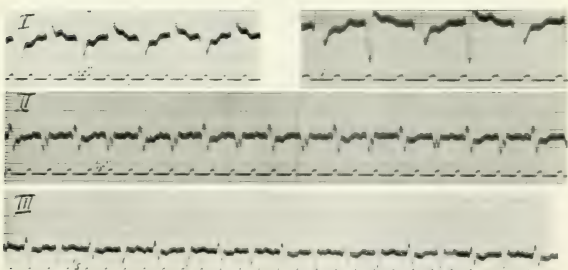


Fig. 3. A regular tachycardia of ventricular origin is seen in which the form of the complexes alternates; the rate is 180 per minute. The first curve in this figure is only standardised; in the case of leads II and III standardisation could not be accomplished owing to the restlessness of the patient.



# OBSERVATIONS UPON THE ACTION OF CERTAIN DRUGS UPON FIBRILLATION OF THE AURICLES.\*

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## ALKALOIDS OF THE CINCHONA SERIES.

IN the first part of this article observations are described which have been carried out with a view to obtaining more precise information upon the action of certain of the cinchona alkaloids, upon the hearts of patients suffering from fibrillation of the auricles. A few words must be said about the preparations used.

*Preparations used.* We are indebted for the preparations of cinchona alkaloids used in the following observations to Messrs. Howard and Sons, of Ilford. Some of our early observations were made with various salts of quinidine (sulphate, bisulphate and bihydrochloride). At a later date Mr. J. W. Blagden and Mr. O. Chick worked specially in Messrs. Howard's laboratories, with a view to obtaining for us pure preparations of certain cinchona alkaloids: they succeeded in preparing the alkaloids quinidine and hydroquinidine with no greater impurity than 0.5 per cent., and with these alkaloids they have very kindly supplied us. They inform us that they believe they are the first workers to have obtained the alkaloids in this state of purity, and that other preparations are frequently contaminated by 20 per cent. or more of impurity. These recent observations of Messrs. Blagden and Chick have revised the measures of optical activity and melting points usually assigned to these substances. The pure dried bases supplied by them and used by us have the following properties:—

	<i>Specific rotation</i> †	<i>Melting point.</i>
Quinidine . . . .	+ 323°, 45'	172.3°C.
Hydroquinidine . . . .	+ 288°, 45'	170.8°C.
Quinine . . . .	— 265°, 0'	172.7°C.

\* Work carried out on behalf of the Medical Research Council. A preliminary account of certain of these observations was given at the Physiological Society, on January 21st, 1922. *Journal of Physiol.* Vol. lvi, vii.

† In experiments upon animals, recorded in this paper, deep anaesthesia (with ether, morphia paraldehyde, or chlorotone) was always employed.

‡ Two grammes anhydrous base dissolved in 5 c.c. HCl of specific gravity 1.16, and made up to 100 c.c. with water at 17°C.

These data have also been supplied by Mr. Blagden and Mr. Chick, whose work on these alkaloids will be the subject of a forthcoming communication to one of the chemical journals.

*Method of testing the alkaloids clinically.* Single test doses of the alkaloid are given, and the effect upon the auricular and ventricular rates are observed. The single doses used have been 0.4, 0.6 or 0.8 of a gramme. In comparing the effects of repeated and equal doses of the same preparation, or in comparing the effects of equal doses of different alkaloids or different salts of one alkaloid, certain precautions are adopted. The patient breakfasts at 6 a.m.; a glass of milk and a slice of bread are given at 8.30; at 10 or 10.30 a.m. the test dose of the alkaloid is given. The patient is connected to the galvanometer and remains lying down quietly for a half hour; records are then begun and these are taken at 10 minute intervals until the drug is given; the patient continues to lie quietly on a couch and the records are continued at 15 or 20 minute intervals throughout a period of hours. The patient is allowed up for a half hour at lunch time (at about 12.30 p.m.\*). In the earlier observations the case was under observation until 6 p.m. of the same day, and morning and evening records were also taken on the second and third days. In later observations this has proved unnecessary and the observations have been ended at 4 p.m. (a 6-hour period).

In these comparative observations every endeavour has been made to keep the conditions as uniform as possible. Thus, in the case of patients recently admitted to the wards, a period of several days or a week's rest has been allowed until the action of the heart becomes uniform. In cases under digitalis at admission, at least 10 days are allowed to elapse before cinchona alkaloids are administered. In patients to whom such alkaloids have not been previously administered a single dose (half the size of the test dose) is given, and on the succeeding day a single dose of the same amount is given morning and afternoon. On the following morning but one the test dose is given and the observations described are made. If the test dose of the alkaloid so given is to be compared with a similar dose of an allied compound, similar preliminary doses of the allied compound are given at similar times relative to the test dose, as on the first occasion. A week intervenes between one test dose and the next.

The records are taken by means of direct leads from the chest wall, two contacts being placed along the sternum and about 4 inches apart.

The readings charted are average readings from the strips of curve; the time period occupied by 10 oscillations in each of the three strips is averaged and the rate calculated. Where the oscillation rate varies materially in any given strip several counts are made and the average is thrown into the general average. The ventricular rate is calculated by

\* This procedure tends to raise the succeeding ventricular reading, but appears to have little or no influence on the auricular readings.



These features of the quinidine curve are summed up in the accompanying chart (Fig. 1) which may be taken to typify the reaction.

The ventricular curve is less easy to describe accurately, for it is subject to much greater fluctuation than the auricular curve. That is so because movement of the patient or excitement has little influence on the auricular rate, while the ventricular rate is very susceptible to such influences. Moreover, the initial rate of the ventricle is more variable than the auricular and its percentage rise is less constant than is the percentage fall of the auricular rate.

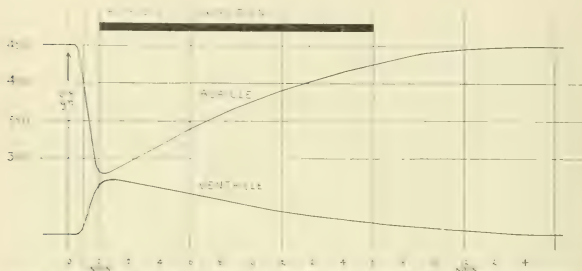


Fig. 1. A diagram of the changes which occur in auricular and ventricular rate in fibrillation of the auricles, when a single test dose of pure quinidine (0.6 or 0.8 of a gramme of the base) is given by the mouth. The dark band above the auricular and ventricular curves represents excretion of the alkaloid in the urine, as tested by Mayer's reagent.

Very frequently the maximal point of the ventricular curve coincides accurately with the minimal point of the auricular curve; the former may come a little before or after the latter. Through and through the ventricular curve moves in an opposite direction to the auricular, there being a fall of ventricular rate during the latter hours of the first day; in not a few charts, however, the ventricular rate is maintained as a plateau for some hours after the minimal auricular rate is reached and passed. Eventually recovery is complete and this complete recovery is reached in the same time as is the auricular recovery.

The alkaloid begins to appear in specimens of urine, passed at frequent intervals, about two hours after the drug is given, that is to say, when the reaction is approaching its height; usually the first specimen to show the alkaloid gives a faint cloud with the reagent; the next specimen taken will show a dense white precipitate, and this continues to be obtained without exception during the remaining six hours of the day's observation. It is the rule to obtain no sign of alkaloid in the urine on the following morning.

though there are frequent exceptions: the urine almost always fails to give a reaction in specimens taken 30 hours after the administration of the drug: in a few instances the reaction in the urine during the second day fails and the alkaloid reappears in a later specimen. Thus, it is the rule for the urine to become free of alkaloid, as tested by this method, some hours before recovery of the heart is complete.

*Absorption of salts of different solubilities.*

The comparative action of different salts of quinidine has been tested in two patients, the preparations used being the sulphate, bisulphate, and bihydrochloride of a commercial quinidine base, contaminated with 16 to 20 per cent. hydroquinidine.\* The solubilities of the salts approximately are:—

Quinidine sulphate	..	..	In 100 parts cold water (15°C).
Quinidine bisulphate	..	..	In 7 .. .. .
Quinidine bihydrochloride	..	In 3.6	„ .. .. .

A standard dose of 0.8 of a gramme of each of these salts was given.† the interval between separate tests being one week. The times and conditions under which the observations were carried out were maintained as constant as possible, records being taken before and after the administration of the drug at approximately 15 or 20 minute intervals. The dose was given at 10 a.m. The curve showing the auricular and ventricular rates were charted. As an illustration Fig. 2 is published.

The initial auricular rate lay in each observation between 418 and 456. The fall of rate began, with each of the three preparations, about half-an-hour after its administration, namely, at about 10.30 a.m., and reached its low limit within 2½ hours of the dose (about 12.30 p.m.). The fall in the bisulphate curve is somewhat delayed in its centre, but otherwise fits well with the sulphate and bihydrochloride curve. The fall, of almost exactly equal extent with the three salts, is to 250 or 260 beats per minute. The remainder of the curves shows the recovery. This takes place slowly: between 12.30 and 6 p.m. there is a gradual rise in rate of about 50 beats per minute. Between 6 p.m. and 10 a.m. of the following morning there is a further recovery of from 50 to 90 beats (the rates now lying between 350 and 400). By the same evening (5 p.m.) the original rates are reached. The three curves are remarkably parallel throughout.

\* These observations were undertaken at a time when we had been unable to obtain a pure preparation of quinidine: for the estimate of impurities we are indebted to Mr. Blagden and Mr. Chick.

† The doses are equivalent to slightly different doses of quinidine base.  
 The sulphate contains .. .. . 0.663 of a gramme.  
 Bisulphate contains .. .. . 0.524 „ „  
 Bihydrochloride contains .. .. . 0.628 „ „

A similar parallelism is shown between the curves of ventricular rate, though these curves (as is the rule) are more irregular. The rise of ventricular rate is coincident with the fall of auricular rate in each instance, and the maximal rise of the former correspond very fairly with the maximal fall in the latter; there is a slight delay (a half-hour) in the height of the ventricular reaction: this delay is probably more apparent than real, for the ventricular curve is more disturbed by the patient's luncheon at 12.30 to 1 p.m.

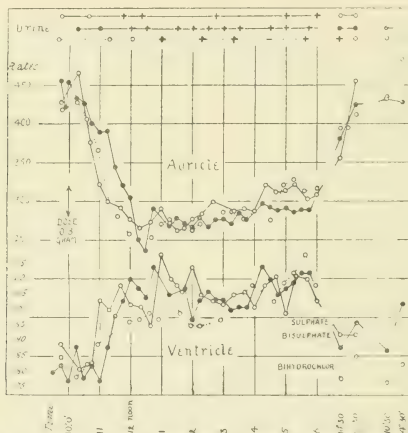


Fig. 2. Case 12. A chart comparing the effects on auricular and ventricular rate of three test doses of commercial quinidine, given in the form of sulphate, bisulphate and dihydrochloride on the 7th, 12th and 19th of September, respectively. The dose of salt was on each occasion 0.8 of a gramme. In this and succeeding charts the upper curves are auricular, and the lower curves ventricular; the corresponding scales of rate are shown to the left; the hours are shown below. In this and the remaining charts, the time at which the doses were given is indicated by an arrow. These are all represented in this chart as given at 10 o'clock; when the dose was given a few minutes before or after the hour, the whole curve has been moved a little to bring it into correct relation to its fellows. This statement applies to succeeding charts also. Above this chart, the presence of alkaloid in the urine is indicated by a + sign, and its absence is indicated by a o sign. The curves are broken where a night elapses.

Above the chart the output of quinidine in the urine is indicated. Specimens were collected as frequently as possible during the first day, and in the morning and evening of the second and third day, and tested by means of Mayer's reagent. The alkaloid appeared in the urine about two hours



after the dose had been given by the mouth, and continued to escape during the whole period of observation. On the morning of the second day a trace of quinidine was found in the urine on the occasion when the bilydrochloride was given.\*

It seems clear from this chart and from the similar set from the second patient (for these curves are very similar to those used as an illustration<sup>‡</sup>), that the three salts of quinidine produce reactions equal in degree and time relations. This similarity was to have been anticipated, seeing that the sulphate and bisulphate are probably rapidly converted to a hydrochloride in the stomach. Such being the case this chart may also be used to illustrate the uniformity of the reaction curves in given patients, submitted at intervals to single doses of the base of approximately equal amount. This uniformity, which indicates the reliability of the curves, is more conspicuous in the case of the auricle than in that of the ventricle; that is so because the ventricular rate is much more subject to the influence of exertion, emotion, etc., than is the auricular, which consequently fluctuates less.

Our observation, that the fall is uniform in degree and rate, when a given quantity of base is administered on more than one occasion to the same patient is not confined to these salts of quinidine. We have on a number of occasions given two doses, at a suitable time interval, of the same salt or same base to the same patient, and have noted very few exceptions to this rule of uniformity. It seems also to be a matter of indifference whether a soluble salt or the base is given; absorption, as indicated by the auricular curve, occurs in the same time. The last statement we make after a comparison of base and salt in several patients, and upon a large number of charts in which base has been given to some patients and salt to others.

#### *Relation between dose and degree of reaction.*

This has been examined in two patients. Separate test doses of 0.2, 0.4, 0.6 and 0.9 of a gramme were given successively on alternate days and the rates were charted. Fig. 3 illustrates this comparison. The falls increase by almost equal increments as the dose is increased; though it is to be noticed that the fall given by 0.4 of a gramme is not of twice the extent of that given by 0.2 of a gramme, and that although the increase from the third to fourth dose is an increase of 0.3 of a gramme, the corresponding fall is not exaggerated. This, and the corresponding curves from the second patient,<sup>‡</sup> suffice to show, however, that with the range of dose here employed,

\* For further information on the output of chemical substances in the urine, see Washington<sup>†</sup>.

† In both patients, as in this case, the reaction to the bisulphate was a little less rapid as compared to that given by the sulphate and hydrochloride forms. This seems to be due to technical accident. In both charts the bisulphate curve comes latest; yet it has the middle solubility.

‡ These are similar, though rather less uniform, the step between the 1st and 2nd, and between the 3rd and 4th curves being about equal to each other, but more extensive than the step between the 2nd and 3rd fall.

there is a sufficiently clear relation between dose and reaction to render approximate quantitative comparisons between different alkaloids or different preparations of these alkaloids possible.

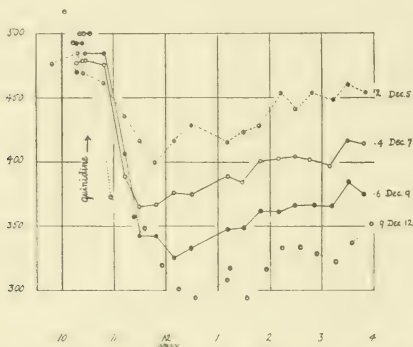


Fig. 3. Case 10. A chart comparing the effects of separate and increasing single doses of quinidine base on the rate of the auricle. The doses were:—December the 5th, 0.2; December the 7th, 0.4; December the 9th, 0.6; and December the 12th, 0.9 of a gramme.

#### *Quinine and quinidine compared.*

It has been stated by Frey<sup>5</sup> that quinidine is more effective than quinine, the alkaloid originally used by Wenckebach, in restoring the normal rhythm in cases of clinical fibrillation. To establish a conclusion of this kind upon the results of treatment in two separate series of cases would not be easy, unless the difference in the power of the two alkaloids was emphatic: for, although both alkaloids, as Frey has shown, are capable of effecting the change to normal rhythm in cases of chronic fibrillation, a fact which we are able to confirm, yet the requisite quantity of one or other varies very much in different patients. If equal quantities of quinine or quinidine are given to two series of patients, and if, in the case of individuals of both series, success is obtained sometimes with relatively small doses, and sometimes only after relatively large doses have been taken, comparison of the effectiveness of the two alkaloids may be difficult unless the two series comprise large numbers of patients. Even if given doses of quinine are administered to a patient without bringing about a restoration of normal rhythm, and subsequently similar doses of quinidine are administered and

the normal rhythm returns, the conclusion that the last alkaloid is more effective than the first in this particular patient, is not fully justified: for here, again, the factor of variation enters: a patient may be given certain quantities of quinidine without apparent result, and later a successful issue may follow a second course of treatment in which smaller quantities of the drug are used.

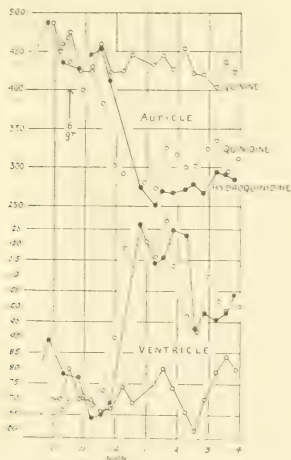


Fig. 4. *Case 1.* A chart comparing the effects of equal test doses of pure Hydroquinidine, quinidine and quinine, given in single doses of 0.6 of a gramme on October the 31st, November the 7th and November the 14th, respectively.

Although, in the end, a general comparison between the power of allied alkaloids might be possible by sufficient repetition, yet this method, used by different workers, would be apt to lead to conflicting conclusions: and it would never be possible to express the relative power in quantitative terms, or to be sure that a statement of difference in action is universally true for all patients.

It has been thought desirable, therefore, to obtain a more simple index of the reaction, and for this purpose we have used single and constant doses of the two alkaloids, following the effect in each case by plotting the subsequent fall of auricular and the rise of ventricular rate; the former, from

this standpoint, is the more valuable of the two. The procedure has been similar to that employed in the case of the different quinidine salts. The pure dried alkaloids have been used in the form of base, and the test dose has been either 0.8 of a gramme (2 cases) or 0.6 of a gramme (4 cases). The comparison has yielded the following result in the 6 cases in which it has been undertaken: the fall of auricular rate is always less with quinine than upon quinidine.

Fig. 4 illustrates this difference well. A single dose of 0.6 of a gramme of pure quinidine base was administered to this patient. The auricular rate stood at 460 before the alkaloid was given: the rate fell quickly, and without break, to a level of 272 per minute, rose a little and continued at an average level of about 319 per minute for several hours. A week later, and under similar conditions, 0.6 of a gramme of pure quinine base was administered. Before the drug was given the auricular rate averaged about 465. This rate fell subsequently to 404, actually the lowest point reached, the general level of rate declining to about 420, a fall of only 45 beats below its original level.

The change in ventricular rate showed an equally striking difference. Starting at a general level of about 70 beats per minute, it rose under quinidine to a general level of about 120 beats per minute, a rise of 50 beats: under quinine the rise in the general level was only just appreciable, though, owing to unsteadiness of the curve, the maximal level reached was 83 beats per minute.

A conspicuous difference in the action of the fibrillating auricle to similar doses of the two alkaloids may be regarded as characteristic, though the degree of difference is subject to variation. The case from which the chart is taken has been summarised: similar summaries of the charts of the remaining 5 cases are also included in the accompanying table (Table I).

The lowest points reached in the auricular rate under quinine is somewhat longer delayed than under quinidine. Fig. 4 shows this: the lowest point in this chart occurs  $4\frac{1}{2}$  hours after the administration of the drug. Usually it occurs at about  $2\frac{1}{2}$  to  $3\frac{1}{2}$  hours after the capsule is swallowed. It is to be noted that in no instance in this series did quinine produce a material change in the ventricular rate.

In addition to these six cases we have given equal doses of quinidine sulphate and quinine sulphate to each of two patients, and have compared their curves. These preparations were impure, the first containing 17 per cent. of hydroquinidine, the last 20 per cent. of cinchonidine. The fall of auricular rate under quinidine was in each case conspicuous, and under quinine was in each case moderate. Though these two observations are of less value, on account of the impurities present, they conform to our general findings.

We conclude that when quinidine and quinine are given in equal doses, the former has a much more powerful effect upon the auricular rate, and that this difference is constant. The quantitative difference in the reaction

TABLE I  
*Comparison of quinidine and quinine.*

Case.	Date.	Alkaloid.	Dose in grains.	Auricular rate.		Venous rate.		Reaction.
				Doses.	Arter.	Extras.	Arter.	
1	Nov. 7	Quinidine	0.6	450	272 <sup>a</sup>	310 <sup>b</sup>	70	120 <sup>c</sup> Conspicuous.
	Nov. 14	Quinine	0.6	465	435	420	70	74 Slight.
2	Nov. 7	Quinidine	0.6	510	298	327	62	87 Conspicuous.
	Nov. 14	Quinine	0.6	498	486	490	58	60 None.
3	Nov. 3	Quinidine	0.8	450	364	300	98	129 Conspicuous.
	Oct. 27	Quinine	0.8	475	370	390	105	160 Moderate.
4	Oct. 21	Quinidine	0.8	520	425	—	—	— Moderate.
	Nov. 3	Quinine	0.8	465	287	335	70	87 Conspicuous.
5	Oct. 27	Quinine	0.8	500	—	440	72	73 Slight.
	Nov. 21	Quinine	0.6	500	334	340	89	120 Conspicuous.
6	Nov. 17	Quinine	0.6	510	480	495	90	97 Slight to moderate.
	Nov. 24	Quinidine	0.6	445	350	330	103	117 Moderate.
7	Nov. 17	Quinine	0.6	485	470	450	95	100 Slight fall.
	Nov. 24	Quinine	0.6	485	470	450	95	100 Slight fall.

<sup>a</sup> Minimal point of initial fall. <sup>b</sup> About 5 hours after dose (normal level).

<sup>c</sup> This reaction to quinidine was quite exceptional in form, and is also the smallest fall upon such a dose that we have seen. We have consequently added the figures of another test dose of quinidine given to the same patient.

<sup>d</sup> General level of plateau.

is variable, usually the quinidine fall is 3, 4, 7 or more times as great as that occurring on quinine: as the first part of the fall is induced more readily than the later phases, quinidine can scarcely be less than 5 or 10 times as powerful as quinine. In respect of the ventricle, while a rise of rate of lesser or greater degree is constant under quinidine, it does not seem to occur under similar single doses of quinine; on occasion the rate may actually fall while the patient is under the influence of the last drug.

### *Quinidine and hydroquinidine compared.*

This comparison has been necessitated especially because in our experimental work<sup>13</sup>, and in the clinical work carried out by Drury and Hiesen, the preparation used was a commercial preparation of quinidine: this commercial preparation was subsequently found to contain 17 per cent. of hydroquinidine. Hydroquinidine is the chief impurity in quinidine preparations, so we are informed, and exists in greater or lesser quantity in all preparations of quinidine now on the market. It was obviously important to ascertain to what extent the action of such preparations owe their action, if any, to this impurity.

The comparison has been carried out on precisely the same lines as the comparison of quinidine and quinine. Six patients (four of whom belonged to the previous series) have been given equal single doses of the two dried alkaloids in the form of base. The results have been sufficiently uniform, and are expressed in Table II, and illustrated by Fig. 4.

The fall of auricular rate and the rise of ventricular rate occur after both alkaloids: the time relations of the curves are essentially the same. The slight delay in the appearance of the hydroquinidine fall in Fig. 4 is not characteristic: it may fall in front or behind the companion curve, or with it. The degree of movement is very similar. We believe that hydroquinidine has, weight for weight, a very slightly more powerful action than quinidine. The difference is admittedly slight: but in all our charts the minimal level reached at the height of the reaction is a little lower for hydroquinidine. These figures are given in Table II, the solitary exception being perhaps *Case 7*. In this patient, although the rule that a lower auricular rate is reached on hydroquinidine was not broken, yet the original rate before the drug was given was lower than was the case in the quinidine test, and, when allowance is made for this original difference, there is little to choose between the two curves. The curve of hydroquinidine usually remains at a slightly lower general level than that of quinidine during the period of recovery. Exceptionally, the two curves cross frequently during the ascent. In only one instance did the hydroquinidine curve ascend at a slightly higher level than that of quinidine. We conclude that in the one patient the reactions were equal; in all the remainder a distinct, though by no means striking, difference between the curves given by the two alkaloids existed. The difference is not so distinct in the ventricular curves.

TABLE II.  
*Comparison of quinidine and hydroquinidine.*

Case.	Date.	Alkaloid.	Dose in grammes.	Auricular rate		Ventricular rate		Reaction.
				Before.	After.	Before.	After.	
1	Nov. 7	Quinidine	0.6	460	272*	70	120§	Very slightly greater.
	Oct. 31	Hydroquinidine	0.6	460	252	83	123	
2	Nov. 7	Quinidine	0.6	510	298	62	87	Very slightly greater.
	Oct. 31	Hydroquinidine	0.6	494	272	58	93	
3	Nov. 3	Quinidine	0.8	455	304	98	129	Very slightly greater.
	Oct. 10	Hydroquinidine	0.8	470	276	95	130	
4	Nov. 3	Quinidine	0.8	465†	287	70	82	Very slightly greater.
	Oct. 10	Hydroquinidine	0.8	510	286	74	90	
7	Nov. 29	Quinidine	0.4	534	393	97	117	Equal
	Nov. 22	Hydroquinidine	0.4	520	372	92	117	
8	Nov. 29	Quinidine	0.4	530	340	72	90	Very slightly greater.
	Nov. 22	Hydroquinidine	0.4	510	304	68	85	

\* Minimal point of initial fall. † About 5 hours after dose (general level). § See footnote, Table I.  
§ General level of plateau.

though in general these also exhibit a slightly more powerful action of hydroquinidine; these curves, fluctuating as they do, are, however, less satisfactory as indices.

In comparing the action of quinidine upon the auricular curve with the action of another member of the same group which has an almost equal power, one point has to be borne in mind. It is conceivable that in a given patient the dose given may be more than sufficient to produce a maximal reaction: were that the case, equal test doses of two alkaloids of different power might produce equal reactions. If a single dose of 0.6 of a gramme of quinidine is given and is repeated later with the intention of adding a second and equal fall of auricular rate to the first, such a second fall is not seen. The second fall is of much less extent than the first (*see* Protocol, *Case 1*). It seems clear therefore that the reaction to the first dose, when this consists of 0.6 to 0.8 of a gramme, begins to approach a maximal reaction. Although, as has been shown, the degree of fall is related to the dose up to these limits, it is improbable that this relation would be maintained much beyond doses of 0.8 of a gramme. Bearing this in mind, in the comparison of quinidine and hydroquinidine, we have more frequently used the small test doses, namely, 0.4 or 0.6 of a gramme, so that the falls of auricular rate might not approach so closely to a possible minimal level.

To sum up, so far as the two alkaloids affect auricular and ventricular rate, it may be said that their action is alike, except that hydroquinidine has, perhaps, weight for weight, a slightly more powerful action. That pure hydroquinidine will produce the final reaction, namely, reversion to the normal rhythm, we have ascertained. In one patient (*Case 21*) a single dose of 0.6 of a gramme produced this change. It seems clear, therefore, that the contamination of quinidine by hydroquinidine will not appreciably influence the reactions obtained by commercial samples of the former alkaloid. This conclusion is not without consequence, for the complete extraction of hydroquinidine from quinidine preparations is not, so we are informed, without difficulty. On the one hand, there appears to be no reason why this purification should be attempted when quinidine is to be used therapeutically: on the other hand, if a pure preparation is desired, the ease with which hydroquinidine is to be obtained in a pure form recommends it as the better alkaloid for standard observations.

#### DIGITALIS, ATROPINE AND QUINIDINE (ALONE OR COMBINED).

##### *Digitalis.*

The action of digitalis, given in full therapeutic doses to patients who display fibrillation of the auricle, is well known in so far as the ventricle is concerned. Given in these doses, namely, a drachm of the tincture for 6 or 10 days, the drug also affects the fibrillating auricle. The oscillations become more rapid, with few exceptions. The rise of rate may be by as much



as 50 or 70 oscillations per minute, though it is often less than these figures, and in a few cases no change is seen. In only one case have we seen a fall of rate, and this in a patient on small doses of the drug.\* The rise of rate is illustrated in several of the present charts (Figs. 12 to 17), and by Table III. This table is composed of average figures of many ventricular rates recorded.

The meaning of the rise of auricular rate, which is the rule, will be discussed subsequently.

TABLE III.

Case.	Before digitalis.		Quantity.		After digitalis.	
	Auricular oscillations.	Ventricular rate.	Drachms.	Days.	Auricular oscillations.	Ventricle.
5	566	107	9	12	624	70
6	471	108	8	11	544	70
7	521	96	9	9	524	50
8	530	77	8	8	600	49
11	463	122	6	8	482	58
12 (1st series)	430	84	5	7	483	54
(2nd series)	430	84	6	8	454	51
13	517	119	11	11	532	65
14	428	129	8	7	467	75
15	510	116	5	10	484	69
16	437	72	7	14	467	55
17	495	125	11½	19	497	73
18	399	90	7	17	395	64

*Digitalis and quinidine combined.*

It has been stated by V. Frey<sup>5</sup>, and by others, that the action of quinidine in restoring normal rhythm in cases of fibrillation of the auricle, is impeded by the simultaneous use of digitalis. If this were the case it would be unfortunate, since many patients while passing under the influence of quinidine are disturbed by a high rate of ventricular beating, and digitalis is capable of controlling this rate. A number of patients whom we have simultaneously treated with digitalis and quinidine have shown a successful

\* In preliminary observations in which small doses ½ drachm of the tincture per diem were given over long periods to out-patients, we were unable to detect any constant change of rate. It appears to be displayed only when full therapeutic doses are given.

reaction, the normal rhythm being restored; but, unless we multiplied our observations many times, it would not be possible to declare whether the percentage of success is greater or less when digitalis is also employed. In one patient (*see* Protocol of Case 26) in whom doses of 0.8 of a gramme of quinidine repeatedly restored the normal rhythm, the same dose was equally effective when the patient was under the influence of digitalis. In view of past statements and the observations to which we have referred,

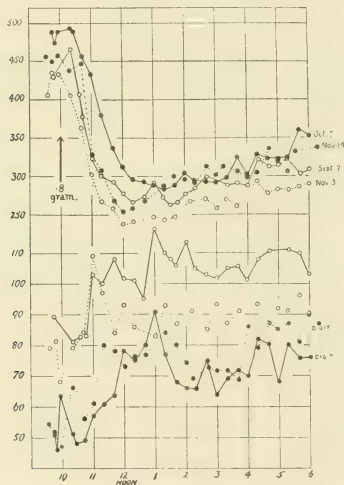


Fig. 5. Case 12. A chart comparing the effects of four doses of 0.8 of a gramme of quinidine sulphate. The two curves of rate represented by black circles were taken while the patient was under digitalis. September the 7th, digitalis free. October the 7th, after the administration of 5 drachms of the tincture in 7 days. November the 3rd, digitalis free for 27 days. November the 14th, after the administration of 6 drachms of tincture in 8 days.

and having regard to the uncertainty in which they still leave us, we have explored the question in a different fashion, comparing the effects of single test doses of quinidine before and after bringing the patient fully under digitalis. These observations are summarised in Table IV, and illustrated by Figs. 5 and 6.

TABLE IV.  
*Quinidine in digitalised and undigitalised patients.*

Case.	Date.	Alkaloid.	Dose in grammes.	Auricular rate.		Ventricular rate.		Amount of "Tinct. digitalis."	Reaction of auricle.
				Before.	After.	Before.	After.		
5	Nov. 10	C. Quinidine	0.6	536	408½	430½	89	132	None.
	Oct. 24			586	436½	438	64	107	
6	Nov. 10	C. Quinidine	0.6	492	324	370	98	118	None.
	Oct. 27			502	360	420	55	86	
7	Nov. 29	Quinidine	0.4	530	392	440	97	125	None.
	Dec. 19			490	400	430	71	87	
8	Nov. 29	Quinidine	0.4	532	338	420	72	102	None.
	Dec. 19			567	375½	420	53	74	
11	Sept. 7	Quinidine sulphate	0.8	488	344	360	117	145	None.
	Oct. 24			540	335	405	61	100	
12	Sept. 7	Quinidine sulphate	0.8	440	262	265	89	118	None.
	Oct. 7			485	283½	292	53	94	
	Nov. 3			425	238	265	77	109	
	Nov. 14			452	253	308	50	84	
13	Jan. 16	Quinidine	0.6	524	376	440	120	137	None.
	Feb. 1			560	500	540	53	70	
14	Feb. 1	Quinidine	0.6	480	290½	300	121	136	None.
	Feb. 13			420	314	355	83	113	

\* C. quinidine = commercial quinidine, contaminated with about 17% of hydroquinidine.  
 † Minimal rate reached. § General level about 5 hours after drug given.

When the patient is fully under digitalis the rate of the auricular oscillations is raised in most patients by some 30 or more beats per minute. Speaking broadly, a single test dose of quinidine now produces a fall or rate which is equal in extent to that obtained by the test dose given in the pre-digitalis stage. Actually, the fall, while the patient is digitalised, may be somewhat diminished, or it may be somewhat increased by the digitalis: the numbers of patients in which a lesser or greater fall is seen are equal. The difference has not been a very conspicuous one, except in a single case (*Case 13*): in this instance, the fall of rate in quinidine was conspicuously greater while the patient was free from digitalis. But because the original

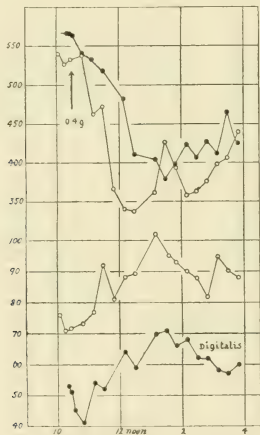
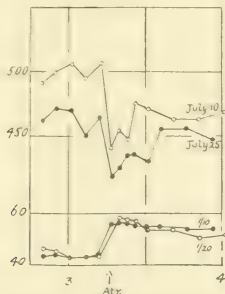


Fig. 6. *Case 8.* A chart comparing the effects of two doses of 0.4 of a gramme of quinidine. The curves of rate, represented by black circles, were taken while the patient was under digitalis. The rates were measured on November the 29th, when the patient was digitalis free; and on December the 19th, when 9 drachms of tincture had been taken in 11 days.

rate of oscillation is higher under digitalis, the lowest rate reached in the quinidine reaction is higher in the digitalised than in the undigitalised subject. Actually, this has been invariable in our cases, though the difference is not often a conspicuous one: it amounts usually to 10, 20 or 30 oscillations per minute. Thus, although it seems clear that digitalis, given in full doses, does counteract the effects of quinidine, it does so in a measure small enough to be compensated by a slight increase in the amount of quinidine given.

The slight disadvantage to the quinidine reaction which follows from simultaneous digitalis therapy is often more than counterbalanced by the control of ventricular rate which is maintained. In the digitalised patient the ventricular rate rises when quinidine is given; often it rises by the same number of beats as in the undigitalised patient, though this is not always so, but it never rises to the same level.

In respect, both of the auricular and the ventricular rates, it may be said that the reaction to quinidine is of much the same extent, whether digitalis has been given or not, but is associated with a somewhat higher scale of auricular rates and a considerably lower scale of ventricular rates in the patient brought under the influence of digitalis.



This action of atropine is the reverse of that accomplished by vagal stimulation; as is well known, the usual effect of such stimulation is to increase the rate of the auricular movements when the auricle is fibrillating, and, generally speaking, the fibrillation continues so long as an increased vagal tone is maintained. It is to be expected, therefore, that atropine, given in cases of fibrillation of the auricle, will slow the oscillations, as these appear in direct leads. This proves generally to be so.

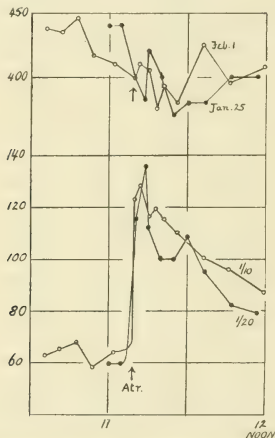


Fig. 8. Case 20. A similar chart to the last. On January the 25th the dose of atropine was 1/20, and on February the 1st it was 1/10 of a grain. A case of fibrillation of the auricle.

The action of atropine upon the fibrillating auricle has been studied in thirteen patients, using doses of from 1/50 to 1/10 of a grain of the sulphate, either hypodermically or intravenously, and its effects are abundantly illustrated in the accompanying charts; when a full dose of atropine is given, the auricular oscillations fall in rate usually by 20 to 40 beats per minute. A distinct fall was seen in 10 out of 13 patients, and in several of these the fall amounted to 50, and in one case to 140 oscillations per minute. In only 3 of the 13 was there little or no appreciable change. The falls of rate are most conspicuous when the drug is injected intravenously, and when doses of 1/20 or 1/10 of a grain are reached. Falls of the usual degree are illustrated in Figs. 7, 8, 10, 15 and 16; Fig. 14 illustrates the occasional patient in whom little change of rate is apparent.

If the same patients are first fully treated with digitalis, the rate of the auricular oscillations is raised, as we have seen: atropine now reduces this rate, the fall being usually greater in extent than in the digitalis free stage. Falls of auricular rate of about equal extent are shown in Fig. 15: falls, which are greater under digitalis, are shown in Figs. 12, 16 and 17. A fall which is conspicuously greater under digitalis is illustrated by Fig. 13: the last chart is an exceptional one.

*Action of atropine upon the ventricular rate, with special reference to the nature of digitalis block.*

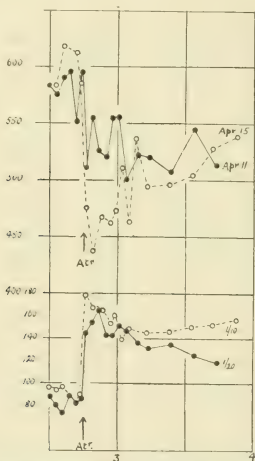
*Historical and introductory.* The slowing of the ventricle, produced in clinical cases of auricular fibrillation by digitalis therapy, is now universally ascribed to block produced at the A-V junction.<sup>7</sup> The precise manner in which this block arises is still under discussion: the evidence is both experimental and clinical. It seems clear that digitalis bodies are capable of producing heart-block in one of two ways, either by an indirect action through the vagus or by a direct action on the muscle. Yet, in many experiments upon dogs, an action on the vagi has been difficult to display. It was well displayed in Traube's original experiments,<sup>22</sup> experiments performed without anaesthetics, and reported in 1871. In recent experiments on dogs<sup>12</sup> and using crystallised strophanthin, we have seen little or no slowing of the heart or block of the ventricle, which could be ascribed to a vagal effect: but we have constantly seen block resulting from a direct action (*see* also experiments on pages 249 and 250).

Variations of the anaesthetic, the use of ether alone, paraldehyde and ether, paraldehyde ether and morphine, have not affected our results: such slowing or block as we have seen has always been due to direct action. Cushny<sup>1</sup> has seen block of vagal origin in dogs, following the injection of strophanthin, under choretone anaesthesia. Robinson and Wilson<sup>17</sup> used cats under ether anaesthesia, and obtained A-V block which, though chiefly of vagal origin, was in part attributable to a direct effect. The results of experiments on animals appear to be complicated by the anaesthetic, and also seem to vary according to the animal used. Thus, experiment has not finally taught us which effect, the direct or the indirect, is predominant in the therapeutic use of digitalis, though it seems to be established experimentally that blocks both of direct and indirect origin occur in various circumstances.

When we examine the clinical evidence, evidence which, if definite, should obviously carry more weight in deciding the question under discussion, we find that this is also conflicting. The argument turns upon the reaction to atropine.

Mackenzie,<sup>14</sup> in 1911, treated cases of auricular fibrillation with digitalis, and reduced the rate of the beating ventricle. In one of these patients a

hypodermic injection of 1.33 of a grain of atropine produced a rise of rate to the level at which it stood before digitalis treatment. Mackenzie speaks of similar results obtained by Silberberg, and concludes that "so far as our observations go, the action of atropine in increasing the rate, when it is slowed, seems to indicate that digitalis acts through the vagus nerve." Silberberg<sup>21</sup> reported a number of observations in the same year, and concludes that the slowing is in part direct and in part vagal; but at a later date this series of cases, to which fresh cases had been added, was reported upon and fully discussed by Cushny, Marris and Silberberg.<sup>2</sup>





by the atropine. This observation does not justify a conclusion that the original fall was vagal in origin, for, if a dose of atropine is given in the predigitalis stage the rate is lifted temporarily to  $a$ . According to Cushny, the original level  $c$  was maintained at a comparatively low point by normal reflex vagal tone, and, when the rate is further reduced (to  $e$ ) by digitalis the subsequent rise on atropine is attributable to the loss of the original vagal tone, prevailing at  $c$  and still maintained after digitalisation, and is not due to the abolition of a digitalis vagal tone. To obtain *proof* that the fall on digitalis is due purely to an increase in pre-existing vagal tone, it would be necessary to show that the rate of the digitalised heart is raised by atropine from level  $e$  to level  $a$ ; since atropine, given in a sufficient dose, should abolish not only the original reflex vagal tone, but also that part of the final vagal tone which has been superadded by digitalis.

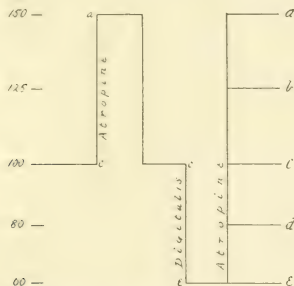


Fig. 10. A diagram used in describing the reaction of the ventricle in auricular fibrillation to digitalis and atropine.

The argument that the final rise under atropine from  $e$  to  $c$  cannot be used as proof of the vagal action of digitalis is evidently sound.

On the other hand, the conclusion of Cushny and his co-workers seems to be carried too far. *Proof* of a purely direct action would be obtained only if the second and adequate dose of atropine failed to produce a rise, namely, if the level remained stationary at  $e$ . It may be argued that since the rise from  $e$  to  $c$  is no greater than the rise from  $c$  to  $a$ , this relation points to both these rises being due to one cause, namely, the loss of the origin reflex vagal tone, and that a digitalis vagal tone plays no part in the fall from  $c$  to  $e$ . This argument is only valid if a certain measure of vagal tone produces equal falls of ventricular rate from different initial levels, and if we can be sure that when the ventricle slows under digitalis, the original measure of reflex vagal

tone is maintained: the first assumption is scarcely justified,\* and the second is decidedly open to question. We conclude that, in the atropine test, proof of uncomplicated vagal action requires a lift of rate from  $c$  to  $a$ , and that proof of uncomplicated direct action requires an unaltered level  $c$ . Neither the one nor the other form of curve characterises the atropine reaction, as this is illustrated by Mackenzie and by Cushny. The rate of the ventricle rises, but it rises either to a level intermediate between  $b$  and  $c$ , or actually to  $c$ .

A question of some consequence to this discussion is what constitutes an adequate dose of atropine in the human subject. In Cushny's series the dose employed was for the most part 1.50 of a grain, given hypodermically. In one patient the test was repeated with 1.25 of a grain and a rise to the same rate of ventricular beating resulted:† from this it was concluded that 1.50 of a grain is a sufficient quantity fully to remove vagal inhibition. This evidence has seemed to us insufficient, it being well known that 1.100 of a grain is inadequate: it has also seemed desirable to investigate the manner in which vagal tone disappears, whether it is an abrupt change or whether partial paralysis may be obtained by regulating the dose. Our preliminary observations have been made upon dogs.

*Minimal adequate doses of atropine.* In three‡ experiments on dogs we have endeavoured to ascertain the minimum dose of atropine sulphate required completely to paralyse the action of the vagus nerve. The vagus is stimulated and its effect on the natural auricular rate observed. As the right vagus has generally a much more powerful influence on the normal rhythm than the left vagus, the first has been utilised exclusively. The rates were measured electrocardiographically, and are expressed in the accompanying table (Table V).

After exposing the vagi and cutting both nerves high in the neck, the right nerve is stimulated repeatedly at intervals to ascertain that constant reactions are present before proceeding. The secondary coil is adjusted at two points on the scale, the near point being such that stimulation yields standstill of the auricle during the period of stimulation,§ the far point being such that an appreciable slowing of the auricle is produced. Constancy being obtained, a record at each distance of the coil is taken and these results are incorporated in the table. Atropine sulphate 0.1 of a milligramme, in a few cubic centimetres of saline are now injected into a vein, and a minute

\* A halving of ventricular rate by block is produced more easily when the rate of the ventricle is initially high than when it is low, and a halving at a high rate means a much larger fall in the number of beats per minute than does halving at a lower rate. It follows that a fall of rate by a given number of beats is much more easily produced when the initial rate is high than when it is low.

† The rise on the 1.25 of a grain was greater than on the 1.50 of a grain, the original level being lower in the former case.

‡ Preliminary experiments to obtain an approximate idea of the dose required are not described.

§ Lasting about 5 seconds.



or a little later the weaker stimulation is repeated and its effects recorded.\* If this weak stimulation still produces appreciable slowing, a second dose of atropine is given: if there is little or no apparent slowing,† the effects of stronger stimulation are also recorded. The experiment proceeds in this fashion, the total amount of atropine injected rises and, as the effects of stimulation become less apparent, the strength of the faradic current is increased.

Experimenting in this fashion, it is shown that in dogs of about 10 kilogrammes weight 0.1 of a milligramme of atropine has usually a very decided effect on the vagus in the direction of paralysing it. But the total dose‡ must be increased to 0.2 or to 0.4 of a milligramme, before the effects of the weaker stimulation are abolished. If the stronger stimulation is now employed, a reaction is still seen and is usually very definite, though standstill of the auricle no longer occurs. Thus, the minimal dose required to abolish decided effects of weak stimulation is insufficient to abolish the effects of stronger stimulation, though the last are materially reduced in their degree.

The minimal dose of atropine required to abolish the effects of strong stimulation is approximately from 0.5 to 1.0 milligramme in dogs of 10 kilogrammes weight, or 0.05 to 0.1 of a milligramme per kilogramme of body weight.

Calculated on this basis for the human subject of 75 kilogrammes, the dose required to paralyse the vagus would be 3.7 to 7.5 milligrammes (or approximately 1/17 to 1/9 of a grain). From these observations upon dogs we should be led to expect that 1.50 of a grain given intravenously in the normal human subject would produce very decided effects on the vagi, nearly but not completely paralysing them, the requisite dose to produce complete paralysis being approximately 1/20 or 1/10 of a grain.

*Clinical observations.* In several cases of auricular fibrillation the releases of ventricular rate obtained by intravenous injections of 1/20 and 1/10 of a grain of atropine have been compared. In two of the patients the ventricular release was no greater with one dose than with the other (Fig. 8), in the third case the ventricular release was slightly but distinctly greater when 1/10 of a grain was injected (Fig. 9) and a more conspicuous difference was recorded in the falls of auricular rate. In a fourth patient complete block was present; in this case the rises of ventricular rate and the falls of auricular rate were equal (Fig. 7). It would appear from these observations that 1/20 of a grain is usually adequate, though on occasion a larger dose is required;

\* All records were repeated once and the table expresses averages of these repeated observations.

† We say apparent because exact measurement of the records has to be left until the plates are developed and dried and the experiment is over.

‡ In speaking of total doses it is to be pointed out that in the later periods of experiments lasting 40 to 50 minutes, there may be some recovery from the effects of the initial doses.

to be quite certain of complete paralysis of the vagus a dose of at least 1·10 of a grain is necessary.\*

Our next observations were upon three patients who were brought fully under the influence of digitalis. In these instances 1·20 of a grain of atropine was injected intravenously, and in each instance a conspicuous rise of ventricular rate was obtained (Figs. 11, 12 and 13). In previous observations, in which for the most part 1·50 of a grain of atropine has been injected subcutaneously, the acceleration of the ventricle, after it has been

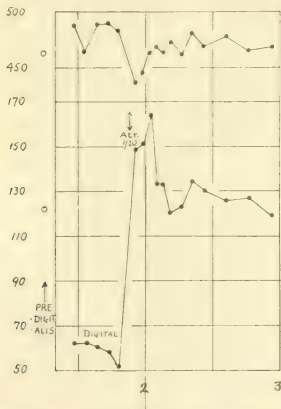


Fig. 11. Case 11. October the 7th. A chart showing the effect of a single dose of 1·20 of a grain of atropine given intravenously to a patient who had taken six drachms of tincture of digitalis in eight days. The average predigitalis rates are shown to the left; auricular rate, 463; ventricular rate, 122.

slowed by digitalis, has failed to pass beyond the original (predigitalis) level. The atropine injection has produced a rise from *e* to *d*, or at the most, from *e* to *c*. Using a heavier dose and injecting intravenously, curves which we regard as more representative are obtained: the rise usually passes beyond the predigitalis level (level *c*) and may go considerably beyond it. Fig. 13

\* This dose is probably as large a dose as it is safe to give: in one patient to whom it was administered, numbness and weakness of the legs, with a little mental confusion, developed temporarily. In the remaining cases dryness of mouth and widely dilated pupils were the chief symptoms.

is the most striking example of our series. In this patient the average rate of the ventricle after a long period of rest in bed was 101 per minute; 1/20 of a grain of atropine raised the rate to 232 per minute. He was now given full doses of tincture of digitalis, taking 9 drachms in 12 days. The ventricular rate fell to an average rate of 70. The atropine injection, being repeated, gave a rise to 205 beats per minute. The first atropine rise was of 131 beats and the second of 135 beats per minute. The full rate of 232 beats per minute was not attained at the second injection, consequently it cannot finally be

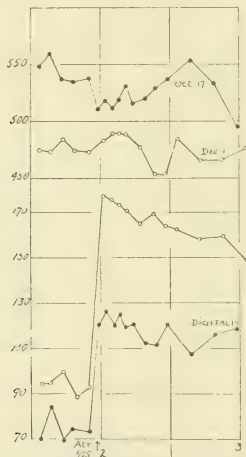


Fig. 12. Case 6. A chart comparing the effects of two separate intravenous doses of 1/25 of a grain of atropine sulphate. On October the 17th the patient was digitalis free, and on December the 1st he had taken 8 drachms of tincture in 11 days. In this and succeeding charts the digitalis curves are represented by black circles, and the digitalis free curves by plain circles.

concluded that the digitalis slowing was in this case purely vagal; but it can be said with some approach to finality that in this case digitalis produced its effect in part, if not largely, through the vagus; for the second dose of atropine almost abolished not only the fall in digitalis, but also the pre-existing reflex vagal tone. The differences of level before and after the administration of digitalis was one of 31 beats per minute; the difference

in the maximal rates attained under the two doses of atropine was one of 27 beats. These two differences cannot reasonably be regarded as equivalent or nearly equivalent: the first difference, occurring at rates above 200, is a minor difference compared with the second, which obtained at rates of 100 and under.

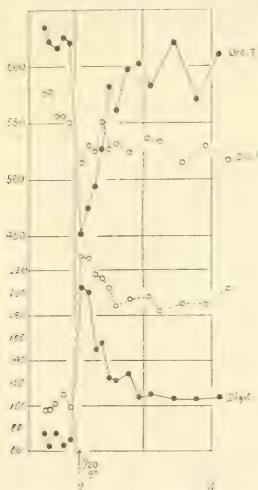


Fig. 13. Case 5. A chart concerning the effects of two separate intravenous doses of 1.20 of a grain of atropine sulphate. On October the 7th the patient had taken 9 drachms of tincture in 12 days. On December the 1st he had taken no digitalis for 49 days.

Finally, in four patients, we have tested the adequacy of such doses as 1.50 or 1.33 of a grain of atropine, given hypodermically, by administering, at the height of the reaction, a second dose sufficient to bring the total dose to 1.20 of a grain. This procedure has been adopted before and after bringing the patient under the influence of digitalis (Figs. 14 to 17). These charts show quite clearly that the hypodermic injections are usually inadequate: they may be adequate as in the predigitalis curve of Fig. 14; more frequently the ventricular rate rises appreciably or conspicuously above its previous maximal point. In these four examples, a new and higher maximal point is always reached in the digitalised patient: \* and it is also clear from the

\* We have seen one instance, and one only, in which this was not the case.

charts that the rise obtained by the second or intravenous dose of the drug is usually greater when the patient is under digitalis than when he is digitalis free. This observation accords with our view that the vagal tone is greater in the digitalis stage, and that, being greater, it is more difficult to abolish by means of atropine.

It is to be observed that in several of these charts the full reaction to the second dose of atropine is not long maintained: recovery is, in general,

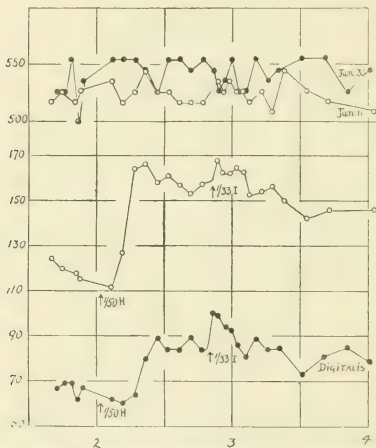


Fig. 14. Case 13. A chart comparing the effects of atropine sulphate given in two successive doses, before and after the administration of digitalis. The first dose was in each instance  $1/50$  of a grain given hypodermically; the second dose of  $1/33$  of a grain was given intravenously during the height of the reaction to the first dose. On January the 11th the patient was digitalis free; on January the 30th he had taken 11 drachms of tincture in 11 days.

relatively rapid. Thus the maximal rate recorded is rarely maintained for more than 2 or 3 minutes, and a conspicuous fall has often taken place within 5 or 10 minutes. We have been careful to ascertain that these rises of rate are not connected with the puncture of the skin or vein, by the needle. Little or no rise of rate occurred in these patients immediately after the hypodermic injections. The instant at which the lift of rate comes is easy to observe by watching the moving string of the galvanometer; it comes, not when the



skin or the vein is punctured, but almost immediately after the actual intravenous injection. We are inclined to attribute the relatively rapid recovery from the maximal rate attained on the second injection, in part at least, to increase in the afferent impulses playing on the vagal centre. The ventricular rate is greatly raised, and we may expect that the vagal centre will, in these circumstances, be called upon to exert itself to the utmost to counteract the excessive heart action: it is unable to do so in whole, because the vagal nerve endings in the heart are damaged by atropine, but it may do so in part.

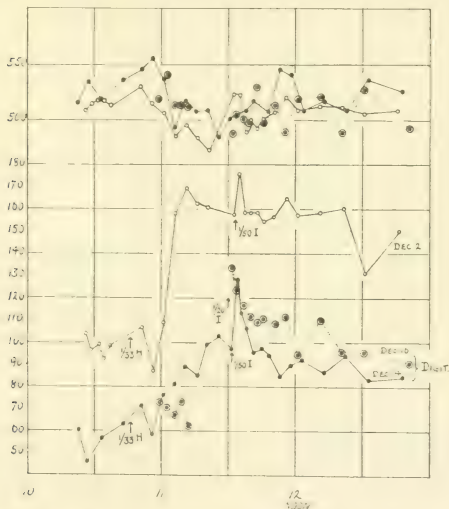


Fig. 15. *Case 7.* A similar chart to the last, to which has been added the effect of a single intravenous dose of  $1/20$  of a grain of atropine sulphate. On December the 2nd the patient was digitalis free, and was given  $1/33$  of a grain of atropine hypodermically, and later  $1/50$  of a grain intravenously. On December the 14th the patient had taken  $9\frac{1}{2}$  drachms of tincture of digitalis in 11 days; he was given similar injections of atropine to those of the 2nd. On December the 16th the patient had taken 11 drachms of the tincture in 13 days; he was given  $1/20$  of a grain of atropine intravenously.

In one instance we have compared the ventricular rates attained by the two doses of atropine, the first of  $1/33$  of a grain given hypodermically and the

second of 1.50 of a grain given intravenously, making a total of 1.20 of a grain, with a single intravenous injection of 1.20 of a grain (Fig. 15). The last method of administration produced a distinctly greater effect. It seems to us probable, that the intravenous method will prove the more effective as a rule, since the height of the reaction to a hypodermic dose is not reached for 20 or 30 minutes after an injection: during this period some of the atropine is probably eliminated or destroyed in the tissues. Figs. 15 and 16 also illustrate the fact that frequently when atropine is given in the digitalis stage, the ventricular rate can be driven above the predigitalis level (level *c* of Fig. 10).

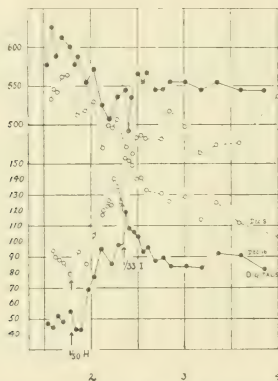


Fig. 16. Case 8. A similar chart to that of Fig. 14. On December the 8th the patient was digitalis free, and was given a hypodermic injection of 1.50 of a grain of atropine sulphate, followed by an intravenous injection of 1/33 of a grain. On December the 16th he had taken  $7\frac{1}{2}$  drachms of tincture of digitalis in 8 days, and received similar doses of atropine to those of the 8th.

In view of such observations as we have now recorded, it seems reasonable to conclude that digitalis does exert an influence through the vagus, and that in greater or lesser measure this increase of vagal tone may be responsible for ventricular slowing. It still cannot be concluded, finally, that the fall of rate is purely vagal in any patient, neither can it be concluded, finally, that the fall is due purely to a direct action in any patient. It seems most probable that both actions are usually exerted, but that they are exerted in different proportion from case to case.

THE THEORY OF CIRCUS MOVEMENT APPLIED TO CERTAIN OF THE  
FOREGOING OBSERVATIONS.

In this article, the effects of certain drugs upon the rate of the auricular oscillations have been recorded. We may now attempt to explain these changes in rate by means of the theory of circus movement. According to our view, each of the oscillations produced by the fibrillating auricle represents a complete circus movement in the auricle, and the average rate of these oscillations in clinical fibrillation, is 450 per minute.\* The rate of these oscillations is determined by the duration of individual circuit movements. The factors governing the circulation time are (*a*) the rate of propagation and (*b*) the length of the path travelled. The length of the path travelled is governed by one or both of two factors, namely, the rate of propagation and the length of the refractory period, according to circumstances. We may say, therefore, that the circulation time is in reality governed by:—

- (*a*) the rate of propagation, and
- (*b*) the length of the refractory period.

A shorter circulation time, an increase in the number of circuit movements per minute, is induced by:—

- (1) an increased rate of conduction (*i.e.*, reduced transmission intervals), and by
- (2) a reduced refractory period, when this permits the wave to accept a shorter channel.†

Conversely, a longer circulation time and fewer circuit movements per minute, are induced by lengthened transmission intervals, and by a lengthened refractory period when the last forces the wave into a longer channel.

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\* In a recent review, Rothberger<sup>1b</sup> appears to be under the impression that there are examples of clinical fibrillation in which the oscillations have a rate of a much higher order. Having examined over 50 cases of fibrillation from this point of view, we are unable to agree. The more rapid oscillations sometimes seen in lead *I I* are either the result of tremor in the somatic muscles, or are due to the plane in which the lead lies; if this is unfavourable, a single circus movement may be represented by several small summits, as shown by Drury and Hassen,<sup>4</sup> just as a single normal auricular contraction may be represented by several summits.

† These are the broad effects, though the question is a complex one. An increase or decrease in the rate of conduction will be mainly, perhaps solely effective, when the original gap is a material one. An increase or decrease in the refractory period will be mainly or solely effective, when the original gap is minute, and the wave is free, at the change, to take a longer or shorter channel.

The path may also change, theoretically, as a result of change in the rate of conduction. If this occurs, the effect of the secondary change would tend to neutralise the effect of the primary change, so far as an influence on rate of circulation is concerned. It is even conceivable that a decreased rate of conduction might lead, by materially shortening the path, to a decrease in circulation time (or an increase of the first to an increase of the second); but these paradoxical effects could only occur in very special circumstances. It is here to be remarked that probably in auricular muscle, responding at a high rate, change in conduction, and in the refractory period never occur apart from one another. Slow conduction appears always to be associated with lengthened refractory period; at all events this is so far as the variations described in the present article are concerned. These two changes, acting in concert, but in opposite directions, tend to neutralise each other so far as they influence the length of path.

To take first of all a simple example, consider the action of the vagus on the fibrillating auricle. Vagal stimulation, acting upon an auricle which is beating at a high rate, is known to shorten the transmission interval and to shorten the refractory period.<sup>10</sup> These changes have the anticipated effect upon the rate of the auricular oscillations; vagal stimulation quickens them.<sup>11, 20</sup> Atropine, by abolishing vagal tone, leads to the reverse changes. It has been shown that, in the auricle beating at high rates, atropinisation impedes conduction and increases the length of the refractory period<sup>10, 13</sup>. As we now show for the clinical case of fibrillation, atropine slows down the oscillations; this effect is at once comprehensible if the theory of circus movement is accepted.

Quinidine has a double action, as have so many bodies which act upon the heart; it has a direct action on the muscle and an indirect action through the vagus. Its direct action, by lengthening the transmission intervals and the refractory period, produces slowing of the auricular oscillations. Its parietic or paralytic effect on the vagus acts in the same directions; thus, the indirect action, like that of atropine\*, tends to slow the oscillations. These effects of vagus, atropine and quinidine may be summed up in tabular form (Table VI).

TABLE VI.  
*Effect of vagus and of certain poisons on the rate of auricular oscillations.*

	Refractory period.	Transmission time.	Duration of circuit movement.	Rate of auricular oscillations.
Vagal stimulation	—	—	—	+
Atropine	+	+	+	
Quinidine (direct action)	+	+	} +	
Quinidine (indirect action)	+	+		
Digitalis (direct action)	+	+	} —	
Digitalis (indirect action)	—	—		+

We come next to the case of digitalis: here the position is less simple. Digitalis, like quinidine, has a double action. It has a direct action on the muscle of the auricle, whereby the transmission intervals and refractory period are lengthened. In so far, therefore, as the direct action is concerned we should expect to find slowing of the oscillations of the fibrillating auricle. But digitalis also exerts an indirect action: it stimulates the vagus, and, stimulating the vagus, shortens both the transmission interval and the refractory period: the indirect action of digitalis will tend, therefore, to

\* Though the end effect is like that of atropine, the last drug acts on the nerve endings, while quinidine, as Dale<sup>2</sup> has recently shown, acts more centrally.

quicken the auricular oscillations. Unlike the action of quinidine, the direct and indirect actions of digitalis are opposed; and the end result depends on which of the two actions predominates.

As has been seen, the usual effect of digitalis upon the oscillations in clinical fibrillation is to quicken them. We see no way of explaining this acceleration, except by supposing that the vagal action of digitalis predominates. A chief obstacle in the way of this conclusion has been Cushing's conclusion that digitalis exerts purely a direct action on the muscle. Largely for this reason we have revised the observations upon the ventricle, and have since been able to conclude that a vagal action is in part responsible for ventricular slowing under digitalis. The objection to our belief that the auricular oscillations are quickened by a vagal action of digitalis is, therefore, largely, if not wholly, removed.

In the case of the ventricle, the direct and indirect actions of digitalis both tend to slow the ventricle; consequently it is difficult to state, in any given case, which action predominates. In the case of the auricle the direct and indirect actions are opposed to each other, and the predominant action is therefore displayed. If our view is correct, then quickening of the auricle is the rule because the vagal action of the drug as a rule predominates. There are cases in which acceleration is not seen, and in these cases we presume that the opposed actions balance. Future observations may show that in a third group digitalis slows the auricle, the direct action predominating. The fact that quickening is not invariable in itself supports our view that opposed actions are in play.

It is, of course, conceivable that the vagal action of digitalis is unequally exerted upon the auricle and upon the tissues which control the rate of the beating ventricle: but there is little evidence that this is so. If there were no such differential action, then it would be anticipated that in the patients in whom the ventricle, submitted to the atropine test, affords the clearest evidence of vagal slowing under digitalis, digitalis should give the greatest acceleration of the auricle; in such a patient also, atropine given while the heart is under digitalis should produce its most conspicuous slowing of the auricle. A comparison of Figs. 13 and 14 suggests that such relations exist. In Fig. 13 we are dealing with the patient in whom atropine raised the rate of the digitalised ventricle to 205 beats per minute: digitalis raised the auricular rate in this patient by 60 beats per minute, and atropine gave an exceptionally large fall of rate. In the second patient, as Fig. 14 shows, the ventricle, when tested with atropine, gave little evidence that the vagus was stimulated by digitalis. Here the rise of auricular rate on digitalis was but slight and atropine exercised little influence on the auricle. The remaining illustrations which are intermediate display these relations less clearly, however, and exceptions in detail are found in them.\* Considering all these

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\* A universal and decisive relationship is scarcely to be anticipated in composite charts constructed in this fashion.

charts together, they favour the views which we have expressed, and, in so far as they affect our main conclusion, namely, that digitalis raises the rate of the auricular oscillations by a predominant action through the vagi, seem to us to confirm it. Such being our conclusion, we apply it also in explaining the now well known power of digitalis to convert clinical flutter of the auricle into fibrillation of the auricle. This action of the drug is evidently of a similar kind to that which we here discuss and seems attributable to an increase of vagal tone.

In a recent case of flutter we have attempted to alter the auricular rate by compressing the vagus in the neck: in the records, and in those previously published by Rihl,<sup>15</sup> Lewis<sup>8</sup> and Ritchie,<sup>16</sup> no change of auricular rate is to be detected. It is probable that the stimulus is insufficiently powerful to produce the change. The rate of the auricular movement in experimental flutter is always raised by vagal stimulation. Levine and Frothingham<sup>6</sup> have recorded a slight change in the rate of the fluttering auricle as a result of forced breathing, and it is noteworthy that the increase of rate accompanied expiration, during which phase of respiration vagal tone increases.

#### INTERRELATIONS OF AURICULAR AND VENTRICULAR RATE.

It is the rule that the rates of the fibrillating auricle, and of the ventricle which responds to it, move in opposite directions, in response to the various influences which are brought to bear on the heart, and which are discussed in this paper. Thus vagal stimulation quickens the auricle and slows the ventricle, atropine and quinidine slow the auricle and quicken the ventricle; digitalis slows the ventricle and quickens the auricle. That this rule may not prove to be invariable is suggested by patients in whom the ventricle is slowed by digitalis, while the auricular rate is unaltered. The meaning of these divergent reactions of the two chambers is to be sought in each instance by detailed consideration of the factors underlying the several movements; but this divergence is sufficiently constant to suggest that the one movement may be dependent upon the other.

#### *Ventricular acceleration under quinidine.*

The meaning of the ventricular acceleration produced by quinidine in fibrillation of the auricle has been discussed in a previous article from the experimental standpoint, and it has been pointed out that two factors are probably concerned in producing acceleration.<sup>13</sup> The first of these is the profound slowing of the auricle, the second is paresis of the vagi. As has been stated, the part played by these two factors in clinical fibrillation cannot be judged by the results of experiment, but must be decided by clinical tests.

That the lowering of rate plays a part is unequivocally shown in some cases when the auricular rate falls to 200 beats per minute.

Thus in one patient and on several occasions when the auricular rate fell to about 200 per minute, and was maintained at or about this level, the patient complained from time to time of sudden attacks of distressing palpitation, and the ventricular rate was found to be at or about 200 per minute. In serial records taken over the period of one such attack, the readings of Table VII (*Case 24*) were shown. The auricles were in a state of almost, if not quite, pure flutter, and when the auricular rate fell from 210 to 200 per minute, the ventricular rate rose abruptly from 105 to 200 per minute. The abrupt rise of ventricular rate was clearly the result of decreased block, consequent on the fall of auricular rate. In *Case 1* of the same table, a mixed response gives place to pure 2:1 response, with a consequent rise

TABLE VII.

*Ventricular response as auricular rate falls under quinidine.*  
(*Extracted from protocols of Cases 1 and 24.*)

Case 1.		Case 24.	
Auricular rate.	Ventricular rate.	Auricular rate.	Ventricular rate.
259	68	222	111
254	63.5	225	112.5
250	72	214	107
234	93	210	105
224	112	200	200
222	111	202	202
218	109	218	109
218	109	220	110
226	113	222	111

of ventricular rate when the auricular rate falls to 224. The part played in the earlier phases of the auricular slowing is more difficult to estimate, though, no doubt, it exists in greater or lesser degree.

To estimate the extent to which vagal paresis contributes to the rise of ventricular rate we have given injections of atropine at the height of the quinidine reaction in four patients.

In two of these patients control curves of quinidine alone were also taken: the charts are illustrated by Fig. 18. Under quinidine alone the ventricular rate rose from 78 to 120. Under the second dose of quinidine, the rate had risen from 78 to 114, when 1.50 of a grain of atropine was given



intravenously. The ventricular rate rose abruptly to 190. In the second patient (*Case 9*) the ventricular rate rose on 0.6 of a gramme of quinidine alone from 85 to 136; on the second dose of quinidine, given a week later, it had risen from 85 to 123, when 1.50 of a grain of atropine, given intravenously, raised the rate to 188. In this patient, as opposed to the first, the auricular rate fell a little in response to the atropine injection. Thus it is clear that a single dose of 0.6 of a gramme of quinidine does not produce anything approaching paralysis of the vagi.

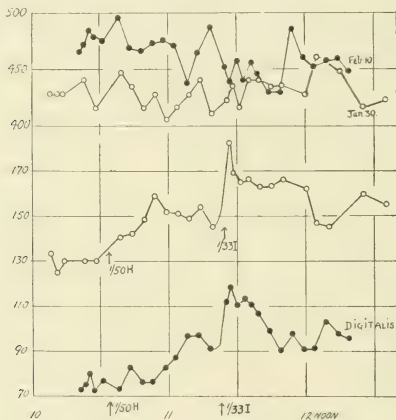


Fig. 17. *Case 14.* A similar chart to the last. On January the 30th the patient was digitalis free, and received 1.50 of a grain of atropine sulphate hypodermically and 1.33 of a grain intravenously. On February the 10th he had taken 8 drachms of tincture of digitalis in 7 days, and received similar doses of atropine to those previously given.

In our experience, a single dose of 1.20 of a grain of atropine almost always produces a greater acceleration of the ventricle than does quinidine in single doses of 0.6 or 0.8 of a gramme, or than quinidine given in repeated therapeutic doses; and this happens despite the much greater lowering of auricular rate which occurs under quinidine; the only exceptions to this rule which we have seen are instances where the auricle passes into flutter on quinidine and a 1:1 rhythm becomes established (as in *Case 24* of Table VII).

In two further patients in addition to the quinidine curves and the combined quinidine and atropine curve, we have recorded also the curve



for atropine alone. Fig. 19, which is illustrative, shows the same points as does Fig. 18. Atropine given at the height of the quinidine reaction produces a conspicuous further rise of ventricular rate.\* Atropine given alone yields a larger and higher rise than does quinidine, but a smaller rise than dose quinidine and atropine combined. The second patient (*Case 23*) gave similar reactions to these here used as an illustration.

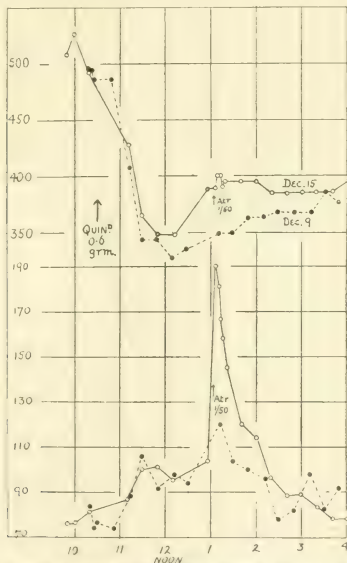


Fig. 18. *Case 10.* A chart showing two curves, each resulting from a single test dose of 0.6 of a gramme of quinidine. On December the 9th (black circles), quinidine only was given. On December the 15th, an intravenous injection of 1.50 of a gramme of atropine was administered at the height of the quinidine reaction.

As a whole these comparisons and the evidence previously given seem to demonstrate that the rise of ventricular rate is in fact due to a combination of the two causes indicated by previous experiments on animals.

\* In this chart, the two doses of quinidine have not given very equal results; the rise on atropine may be judged, however, from the curve of February 15th, alone.

An unexpected feature of the curves has been the failure of the auricle to respond to atropine by slowing, while the heart is deeply influenced by quinidine. With one possible and slight exception no change of rate, which could not be ascribed to natural fluctuation of the curve, has been seen in any of the four cases. Unless quinidine has a greater effect on that part of the vagal apparatus which supplies the auricle than upon that which supplies the junctional tissues we are unable to account for the failure of the

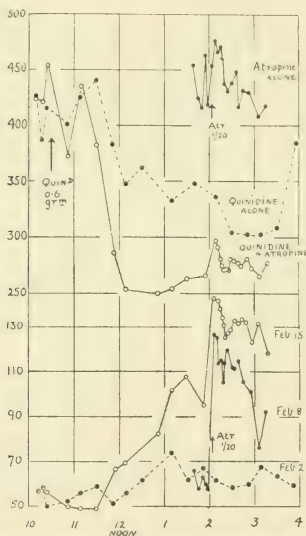


Fig. 19. Case 22. A similar chart to the last, to which has been added an atropine control curve. On February the 2nd (dark circles and broken line) a dose of 0.6 of a gramme of quinidine was given. On February the 15th (clear circles) a similar dose of quinidine was followed by an intravenous injection of 1/20 of a grain of atropine. On February the 8th, an intravenous dose of 1/20 of a grain of atropine was given and nothing else.

usual reaction. It had been hoped that atropine would exaggerate the reaction of the auricle to quinidine, and might prove of value therapeutically; in so far as we have investigated the combined reaction, we have seen no evidence that this is to be expected.

*A-V block produced by quinidine.* Experimental work has shown that quinidine, given in doses equivalent to those used clinically, produces a certain measure of *A-V* block. Such block, if it occurred clinically, would in some measure check the rise of ventricular rate for which quinidine is otherwise responsible. That the degree of block so produced is not considerable, is shown by those cases in which the auricular rate falls to a relatively

TABLE VIII.

	Date.	"P-R" interval at restoration, and later.	"T" in lead II.	Probable duration of A.F.	Total quinidine dosege.
Case I	24.8.21*	0.19	Semi inverted	18 months	2.4 grammes in 2 days.
	8.9.21	0.16	Upright		
Case 10	16/12.21*	0.21	Inverted, slight	11 months	2.2 grammes in 2 days.
	17/12.21	0.19	Upright, prominent		
S.†	22.7.21*	0.17	Deeply inverted	4 years	2.0 grammes in 2 days.
	23.8.21	0.16	Upright, slight		
No.†	28/7.21*	0.18	Upright, slight	4 years	6.6 grammes in 4 days.
	2/8.21	0.17	More upright		
	29/8.21	0.16	Upright, prominent		
A.†	11/8.21*	0.22	Upright, slight	15 months	4.4 grammes in 4 days.
	15/8.21	0.19	Upright, prominent		
	19/9.21	0.18	Upright, prominent		
W.†	17/8.21*	0.20	Upright, slight	2 months	2.8 grammes in 3 days.
	25.8.21	0.17	Upright, prominent		
H.	27/8.21*	0.23	Upright, slight	3½ years	2.8 grammes in 2 days.
	19/9.21	0.18	Upright, slight		

\* Date on which normal rhythm became restored.

† Cases VIII, X, XI and XII respectively of Drury and Hiescu (Brit. Med. Journ., 1921, II, 511).

low level and a 1 : 1 response of the ventricle is developed. But that a slight grade of *A-V* block does develop clinically is clearly evidenced in cases in which the normal rhythm is restored. Immediately after the normal rhythm is resumed the *P-R* intervals, estimated in curves from lead II, are usually

somewhat longer than are the intervals in the same curves a day or so later. This recovery of natural conduction in patients is displayed in Table VIII.

This factor of A-F block, in some measure disturbs our estimates of the individual parts played by vagal paresis and lowered auricular rate in producing the ventricular acceleration of quinidine poisoning: the block is due to a direct action on the muscle. The rise produced by atropine alone (Fig. 19) may fully represent the release of vagal tone; but the rise under quinidine only and the combined rise under quinidine and atropine do not represent the full effect of lowered auricular rate and a partial or complete release of vagal tone. For in both these instances the rise of rate is counteracted by the direct action of quinidine on the junctional tissues.

*Ventricular slowing under digitalis.* In discussing the nature of the ventricular slowing which is produced by digitalis, it is usual to assume that the action of the auricle is unaltered by digitalis, and that the fall of ventricular rate is due purely to an effect on the junctional tissues. Now this is not true, strictly speaking, for digitalis as a rule quickens the beating of the auricle, and this quickening of the auricle may in itself tend to slow the action of the ventricle. The rise of auricular rate being relatively small and occurring at very high rates of auricular beating probably does not influence the ventricular rate materially. In experiments on dogs in which the auricles are faradised and the auricular and ventricular rates are recorded, conspicuous variations are often witnessed in the auricular rate without there being corresponding changes in ventricular rate. In our experience it is only when the auricular rate falls in the dog to levels of 350 or less, per minute, that the divergent movement of rates begins to be manifest. The protocols of the experiments recorded in the next paragraph sufficiently illustrate this statement. It is probable that the rise of auricular rate, when digitalis is given in clinical fibrillation, has little influence on the reaction of the ventricle.

*Further observations relevant to the reaction of the ventricle in auricular fibrillation to digitalis and atropine.*

In a series of experiments upon dogs, previously reported,<sup>12</sup> we were unable to obtain any evidence of heart-block on injecting strophanthin, other than that due to a direct action on the muscle of the heart. In subsequent experiments we were inclined to attribute the lack of vagal effect to our anæsthetic. The following experiments were performed primarily with the idea that by varying the anæsthetic, an increase of vagal tone might be obtained with strophanthin, and also with the idea of obtaining a reaction of the fibrillation *auricle* to strophanthin, similar to that which we observed when digitalis was given clinically, namely acceleration. In neither of these objects were we successful: but the results of the experiments are relevant to several questions previously discussed in this article.

As, in the previous series, crystalline *g*-strophanthin in small doses was employed. Three of our experiments are utilised. In two of these both the auricular and ventricular rates were recorded galvanometrically: leading direct from the auricle for the former, and from the limbs for the latter. In

<i>Dog O C (kilo 13-1).</i>			<i>Dog O D (kilo 8-1).</i>		
<i>Anæsthetised with morphine, paraldehyde and ether.</i>			<i>Anæsthetised with paraldehyde and ether, the latter in small quantities.</i>		
Time.	Aur. rate.	Ventr. rate.	Time.	Aur. rate.	Ventr. rate.
12.17	515	288	11.46	539	264
12.17½	456	292*	11.48	564	282*
12.26	511	286	11.53½	585	279
12.34½	491	196	11.55	585	265
12.36	425	352	12.03	632	275
12.41½	494	292	12.03½	587	267
12.45	0.13 mg. strophanthin		12.11	382	295
12.51	327	294	12.14½	527	262
12.58	360	254	12.24½	691	369
1.08	331	269	12.30½	900	234
1.14	312	312	12.36	484	245
1.22	318	297	12.42	667	266
1.32½	276	276	12.47½	0.065 mg. strophanthin	
1.45	400	250	12.52	484	234
2.02	424	268	12.55	492	244
2.16	420	272	1.01½	468	234
2.31	416	272	1.11	475	237
2.45	413		1.22	495	245
2.47	0.13 mg. strophanthin		1.30	0.065 mg. strophanthin	
2.52	403	227	4.72		240
2.57	358	234	1.40	500	248
2.58	372	261	1.48	454	246
3.11	414	278	1.58	458	234
3.22	357	238	2.03	0.065 mg. strophanthin	
3.37	417	276	2.11	452	226
3.40	0.65 mg. atropine		2.19	452	228
3.42	359	222	2.19½	465	233
3.45	306	228	2.21	0.065 mg. strophanthin	
			2.27	403	218
			2.41	392	219
			2.50½	394	210
			3.01	387	192
			3.03	0.065 mg. atropine	
			3.08	241	241
			3.16	282	222

\* *Italic* = after-effects consisting of fibrillation. The italicised readings should be compared with themselves, and not with the unitalicised readings.

\* *Italics* = after-effects consisting of impure flutter.

the third experiment, in which ether was the only anæsthetic, the chest was left unopened and the ventricular rates were alone obtained. In all three experiments the auricle was stimulated faradically, and the rates were studied (1) while the auricle responded to this current and (2) wherever possible during continued after-effects of stimulation. The rates in the second

circumstance were particularly desired, because the after-effect is alone comparable to the clinical condition.\* These after-effects are not always to be obtained, however; especially is this the case after strophanthin has been injected in the circumstances of our experiments.

*Inter-relation of auricular and ventricular rates.* During faradisation the rate of auricular beating, at a point as far removed as possible from the point stimulated (*i.e.*, the auricular appendix),† varies a good deal from

*Dog O F (kilo 16.2).  
Anæsthetised with ether. Thorax unopened.*

Time.	Ventricular rates.		
	Normal rhythm.	Under stimulation.	During after-effects.
11.42	—	255	—
11.49	169	240	264
11.55	—	—	247
12.03	193	278	—
12.04½	—	—	286
12.11½	195	269	253
12.15	0.13 mg. strophanthin	—	—
12.20	185	268	260
12.29	110	276	254
12.34	192	290	278
12.38	0.13 mg. strophanthin	—	—
12.45½	169	242	—
12.56	181	269	—
1.04	194	290	322
1.09	218	294	308
1.13	0.13 mg. strophanthin	—	—
1.19½	193	284	286
1.24½	191	261	256
1.28	202	274	265
1.34	0.25 mg. strophanthin	—	—
1.41½	172	222	—
1.47	240	236	—
1.52	—	—	230
1.57	0.65 mg. atropine	—	—
1.59	183	150	—

moment to moment. As in the early readings of the one experiment (*Dog O D*), there may be a tendency for the ventricular rate to fall when the auricular rate rises, but this opposite movement of the ventricular rate is neither conspicuous nor constant, when the auricular rate is very high. But if the auricular rate is lowered, and falls very much (as in *Dog O C* to

\* In many past writings on fibrillation of the auricle, it has been assumed that the disorder of the auricle, occurring while this chamber is being faradised, is equivalent to the clinical condition. That is not the case for, while under stimulation, the muscle actually stimulated is in a state of rapid re-excitation and the rest of the auricle responds to this.<sup>9</sup>

† In the third experiment, in which the thorax was unopened, we stimulated the mouth of the superior cava by means of electrodes introduced through the superior cava. This experiment was intended to ascertain if an increased vagal tone under strophanthin is prevented by the opening of thorax and pericardium.

312 per minute), the ventricle may assume the full auricular rate and the lift may then be conspicuous.

*Reaction of the auricle to strophanthin.* It was hoped that a reaction similar to that of the fibrillating auricle to digitalis which is seen clinically, might be obtained, and that it might be further investigated. Such a reaction was not obtained; on the contrary, the strophanthin injections reduced the rate of the auricle (both while it was responding to the faradic current, and in the after-effects when these were seen) and tended to abolish after-effects. These effects are ascribed to the direct action of strophanthin in our experiments, by which it lengthens the refractory period<sup>12</sup> of the muscle.\*

*Reaction of the ventricle to strophanthin.* With few exceptions a slowing of the ventricle was seen after the injection of strophanthin. This slowing appears to have been due purely to a direct action of the drug, as in our previously recorded experiments. The degree of slowing was definite, but not conspicuous; it is more noteworthy, however, because it was obtained with very small doses of strophanthin (1/8th or 1/16th of a milligram), and because it occurred despite a simultaneous decrease of auricular rate.†

*Reaction to atropine.* When the heart is under the influence of strophanthin in the circumstances of our experiments, and atropine is injected, the auricular rate falls and may fall conspicuously. This reaction in these experiments is in accord with past observations, and is ascribed to lengthening of the refractory period in the auricular muscle. The *ventricular rate also falls* (*Dog O C* and *O F* illustrate this fact) unless the simultaneous fall of auricular rate procures a 1 : 1 response of the ventricle (as in *Dog O D*). The fall of ventricular rate here observed finds its counterpart in our previous observations upon atropine, in which the auricle was beating rapidly in response to rhythmic shocks.<sup>12</sup> No doubt the reaction described is associated in some way with the weak vagal tone prevailing in our experiments; it belongs to the series of paradoxical reactions to vagal stimulation which we have already placed on record.<sup>12</sup>

The lowering of ventricular rate by atropine in the dog's heart under strophanthin is more noteworthy in that it may occur despite a simultaneous lowering of auricular rate.‡

\* The reverse, and clinically predominant, vagal effects being absent.

† The tendency of which is to increase the ventricular rate.

‡ The latter tending to raise ventricular rate. The question naturally arises as to whether or not a similar factor sometimes comes into play when atropine is given in clinical cases of fibrillation under the influence of digitalis. If it does do so, then the rise of ventricular rate under the atropine test, discussed in an earlier part of this paper, could not be regarded as the full measure of vagal tone then prevailing. It seems to us improbable, however, that any material fallacy can arise from this source; we should be more inclined to suspect such fallacy if atropine injections sometimes produced an actual fall of ventricle rate when given in clinical cases of fibrillation under digitalis.

OBSERVATIONS RELATING TO THE DIFFERENCE IN THE NATURE OF  
FLUTTER AND FIBRILLATION.

When pure flutter and fibrillation are examined either clinically or in experiment, the outstanding differences between these two disorders are the greater rate at which the auricle beats and the unevenness and variation of conduction in the latter. According to our views, the first observed difference, namely, the higher rate of beating in fibrillation is due to the circus movement being completed more rapidly. The short circulation time in fibrillation is attributable, according to the theory we support, either to more rapid conduction or to a shorter path.

It is very difficult to assume more rapid conduction as the explanation, for the faster the auricle beats the slower it conducts: so, if we are to suppose that the wave is propagated at different speeds in fibrillation and flutter, it would be necessary to suppose that the speed is greater in flutter. This argument would lose force if we dealt simply with fibrillation in one patient and with flutter in another; in these circumstances the properties of the auricular tissues in the two cases might dictate the mechanism. It happens that both pure flutter and fibrillation can occur as stable mechanisms in one and the same case at different times, and under external conditions which appear to be identical. Thus, long continued flutter is sometimes converted into fibrillation by digitalis, and this fibrillation may continue long after the influence of digitalis has been withdrawn. Moreover, old standing fibrillation may sometimes be converted to pure flutter by means of quinidine, and this flutter is continued long after the effects of quinidine have vanished (Protocols of Cases 1, 24 and 25). It would be unreasonable to assume that these drugs permanently alter the rate of conduction in the auricle. A second and strong argument against faster conduction in fibrillation is the irregularity of conduction in this condition; for this irregularity of conduction is shown by experiment to consort with conduction heavily strained. It may be assumed safely, therefore, that conduction is if anything slower in fibrillation than it is in flutter. Since such a difference would account for a slower, but could not account for a faster rate of beating in fibrillation, we are forced to the only alternative conclusion, namely, that in fibrillation the path is shorter.

A shorter path in fibrillation might be attributed to a short refractory period.\* This view of the refractory period is held by Rothberger and Winterberg,<sup>20</sup> and is consistent with the relation between refractory period and rate of beating, the former becoming shorter as the rate rises. We think it probable that the refractory period is shorter in fibrillation than in flutter, but this distinction would not by itself explain irregular conduction in fibrillation.

\* It might also be attributed to slower conduction, but a shorter path, consequent upon slower conduction, would not explain a shortened circulation time.



In fibrillation the path may be shorter than in flutter for another reason; the gap between the crest and wake of the circulating wave may be shorter in fibrillation. This is our present view of the essential distinction between the two disorders, and we arrive at this conclusion because, assuming a short gap in fibrillation, we should at once explain why conduction is irregular and varying: the tissue into which the wave enters has little chance of recovery beforehand. Assume the presence of an appreciable gap in pure flutter, and there would be an appreciable time for recovery and the power of the tissue to conduct would improve and become more uniform. A longer gap in flutter, other factors being unchanged, would mean a longer path and a slower circulation time; thus its assumption would explain those characteristics of flutter which distinguish it from fibrillation. Accept this view as a working hypothesis and it follows that the path followed by the wave in flutter is a path which it is compelled to travel; it remains to explain why the crest of the wave is unable to make a short cut and thus to approach more closely to its own wake. To picture our conception in more detail imagine a circus movement around the mouths of the superior and inferior vena cava. Such a circulating wave may be stable even though an appreciable gap exists. The short path between the cavæ cannot be travelled because, when the crest of the wave arrives opposite this bridge, it will always find the muscle on the far side of this bridge refractory. Suppose that, when such are the conditions, the refractory period of the muscle is shortened by such interference as vagal stimulation. The gap may now widen so far as to leave the bridge clear, the short cut will be taken and the wave will now circulate, with a much shortened gap, around one or other cava. Consequent on this change the circulation time will decrease\* and, in response, the refractory period will shorten a little more; thus the new mechanism will tend to become stabilised even though the original influence, which shortens the refractory period, passes away. In the new mechanism, the gap will be shorter, and conduction will be more irregular and a little slower. In this way we would explain the change from stable flutter to stable fibrillation. Follow the process in the reverse direction and the change from stable fibrillation to stable flutter is explained.

Now the last change occurs in some cases of fibrillation treated with quinidine, and here the steps may be followed in some detail. When quinidine is given to cases of fibrillation, a state of impure flutter is always developed as the auricle slows down; withdraw the quinidine at this stage and the auricle speedily reverts to its original condition of fibrillation. In perhaps one case in ten or more, when the rate falls to about 200 per minute, there is a new and seemingly abrupt change; *pure flutter* develops. The significance of this change has not as yet been appreciated; for if the quinidine is now withdrawn, the mechanism does not revert, but pure flutter persists (Protocols of Cases 1, 24 and 25). The mechanism is recognised as

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\* The change being relatively abrupt.

pure flutter because the auricular complexes have become quite regular and because the responses of the ventricle to individual auricular beats are now manifest.

It is known that the auricle of such a patient while under quinidine has an increased refractory period and increased transmission intervals, and to these the changed mechanism is attributed; but we are bound to acknowledge that a day or two after withdrawing the quinidine the refractory period and conduction power are again what they were before quinidine was given. Thus, although both factors which tended to slow the circus movement disappear, little acceleration is apparent. It is obvious that the crest of the wave can no longer be following its own wake: a material gap must have opened up. After the lapse of a week or more, the pure flutter still continues: if quinidine is administered again to this patient while the flutter is stable, considerable doses may be given without appreciably affecting the rate of the oscillations (Protocol, *Case 1*). The delay in obtaining a pronounced fall of rate is due to the period during which the gap is closing up, as the refractory period lengthens.

When pure flutter first becomes established, there is a little quickening of its rate during the period of recovery from quinidine (Protocol, *Cases 1 and 25*): similarly, if quinidine is given afresh while this stable flutter persists, there is a little slowing of its rate (Protocol, *Case 1*): but neither of these changes are conspicuous. We attribute both purely to change in conduction, and do not believe that change in the length of the refractory period plays any part in it. If this view is a correct one, then cases of this kind permit us to assess approximately the proportion in which lengthened transmission intervals on the one hand, and lengthened refractory period on the other hand, are responsible for slowing when these cases of fibrillation are treated with quinidine. It would obviously be concluded that lengthened refractory periods plays the chief part in these cases.

#### ABNORMAL VENTRICULAR COMPLEXES.

During the quinidine treatment of auricular fibrillation, abnormal ventricular complexes are frequent in electrocardiograms. These may be single, or may occur in pairs or small groups. These abnormal complexes are seen in about one case in three or four of those who are treated with quinidine and who failed to show them before treatment. In occasional cases they become very numerous and are then associated with short or long periods of ventricular tachycardia.

The abnormal beats, resulting from quinidine, occur almost exclusively at the height of the auricular reaction, namely, when the auricular rate has slowed down considerably. Thus, in susceptible cases, they have not been seen at rates over 400, they occur only very occasionally at rates above 350; from 350 downwards they become more and more numerous and are most frequent at rates of 250 to 300. When, as sometimes happens, the auricular mechanism changes to pure flutter, they seem to disappear

entirely. Thus, the abnormal beats are definitely associated with a stage of quinidine poisoning during which the heart is profoundly influenced by the alkaloid, and they occur unerringly over only a small range of auricular rates, disappearing again, if the drug is discontinued, when the auricular rate rises above the favoured levels. Judging from curves taken directly from the chest wall, either ventricle may be involved, the abnormal complexes having a chief upward or a chief downward phase. In any given case the type is as a rule constant, though occasionally both types may be seen in the same case (Fig. 20*f*), one or other strongly predominating.

When the rate of ventricular is slow, the abnormal complexes are always the most premature in the curves, but they do not occur at fixed intervals after the beats which precede them as is usual in the case of similar abnormal complexes in the condition described as "digitalis coupling." The relation between abnormality of outline and prematurity, which undoubtedly exists when the ventricle responds slowly, is susceptible of alternate explanations. Either the beats are premature because they are abnormal (extrasystoles), or they are abnormal in form because they are premature (aberrant beats). The second explanation has been adopted by White,<sup>24</sup> though we think without full justification. There are numerous examples in which the second explanation appears to be untenable, and these occur especially when the rate of the ventricle is faster. In such circumstances, although the abnormal beats still tend to be premature in the average, yet they are not necessarily the most premature beats in the curves, and a clear relation between prematurity and abnormality of outline is not discovered. Thus in Fig. 20*a* the abnormal complex (*x*) does not represent the most premature beat of the curve, the diastole preceding beat marked *y* is shorter. Fig. 20*b* illustrates the same point, the beats marked *y* being more premature than the abnormal beat *x*. In Fig. 20*c* is a group of four abnormal beats, alternating in amplitude, but here, again, other beats of more normal outline occur after shorter diastoles.

Longer runs of abnormal beats are shown in Fig. 20, *d* and *e*; two curves which were taken from a single case. In this instance an almost regular tachycardia becomes established, the ventricle beating at a rate of 140-150 per minute. As to whether these rapid beats are responses to auricular impulses it was not possible to decide in individual curves, for the auricle did not beat quite regularly; it was in a state of impure flutter. But since, in such groups of abnormal beats, the heart action tends to become regular, and since a relation between abnormality and prematurity so often fails, we incline definitely to the view that these abnormal complexes are not to be regarded as aberrant forms, but that they are more comparable to the abnormal beats which help to constitute the digitalis coupling. However, actual coupling, such as is seen under digitalis, has not been seen under quinidine: probably because in digitalis therapy the ventricle slows, while under quinidine it accelerates. If we are right in assuming that we are dealing with beats of a similar order to those seen under digitalis, a reason for their appearance

under the influence of these two poisons has to be suggested. Quinidine and digitalis both prolong the refractory period and lengthen the transmission intervals of heart muscle.\* We suggest that the abnormal beats occurring under each form of poisoning are in some way associated with alterations of the muscular excitability; an alteration which is not in the direction of an exaltation but in the direction of depression. That the new beats are associated in some way with the constitution of the refractory period is strongly suggested to us by an observation upon a patient who was under the influence of quinidine, and to whom an intravenous injection of atropine was given. Immediately after the atropine was injected, short runs of abnormal beats were seen; in these curves also it could be shown that the beats were not abnormal *because* they were premature, other beats of natural outline occurring in the same curves and after shorter pauses. Atropine is known to alter the refractory period, lengthening it and, by so doing, prolonging the conduction intervals.

In this connection we remember that there is some evidence to suggest that certain premature beats may be reentrant beats; that one beat sets up a second in this fashion. This possibility has been briefly discussed in a previous paper.† This idea, so it seems to us, must be borne in mind; especially so since over-doses of digitalis are thought to give rise to a circulating mechanism in the ventricle, namely, to fibrillation of the ventricles. The real nature of the extrasystole is still unknown; it may be that in some instances we are dealing with reentrant beats, and this idea would seem most naturally applicable to instances of accurate coupling, such as occur under digitalis, or to instances where a rapid and almost regular rhythm seems to emanate from the ventricle, a phenomenon seen both under digitalis and quinidine. It is finally to be remarked that a remedy such as quinidine, which tends to bring auricular fibrillation to an end, is not necessarily one which, given in smaller doses, tends to ward off such fibrillation; the contrary may be the case.

*Protocols of case notes.*

In the following protocols, we give a brief summary of the patients' histories and physical signs at the time when the observations were made. In doing so we abbreviate. Under congestion, the state of the venous system is summarised. No congestion means that the veins and liver were normal; slight congestion signifies some engorgement of the veins and cyanosis, with or without slight enlargement of the liver. The size of the heart is described as not enlarged or as slight but definitely, moderately or considerably enlarged, according to the grade of enlargement. By poor exercise tolerance we mean that symptoms of distress are observed to arise after exercise equivalent to walking up a short flight of stairs; by fair exercise tolerance we mean that distress is produced by exercises equivalent to walking briskly upstairs or hurrying on the level; by good tolerance we mean that the last exercises are accomplished without trouble. The remainder of the protocols consist of extracts of the notes and observations which are relevant to the text of our article.

*Case 1.* J. P. A man, aged 37. Admitted October the 21st, 1921. No history of rheumatic fever. Cardiac symptoms for 6 years. Mitral stenosis and auricular fibrillation, the last known to have been present for 18 months. Signs of slight congestion. Heart slightly but definitely enlarged. Poor exercise tolerance. Observations on this case will be found in Tables I, II, VII and VIII, in Fig. 4, and in the detailed observations which follow.

\* Digitalis, acting on the auricle, both directly and indirectly, shortens the refractory period; but acting on the ventricle the direct action will be almost unopposed.

† *Heart*, 1918-20, vii, 247 (Fig. 18 and explanation, especially).

Date and time.	Auricular rate.	Ventricular rate.	Remarks.
Nov. 21 9.35	476	67	Fibrillation of the auricles; control curves taken before the administration of quinidine.
9.43	476	75	
9.46	476	78	
10.20	484	71	
10.40	484	64	
11.0	476	78	
11.20	469	59	Fall of auricular rate and rise of ventricular rate. Fibrillation passing into impure flutter under quinidine.
11.40	448	65	
12 noon	Quinidine 0.6 gr.		
12.1	484	67	
12.20	423	73	
12.40	385	90	
1.0	319	107	A second dose of quinidine at first adds little to the reaction.
1.20	306	118	
1.40	270	115	
2.0	291	127	
2.20	291	105	
2.40	265	110	
3.0	Quinidine 0.6 gr.		The auricular rate falls a little, and the ventricular rate is greatly raised by tachycardia of seeming ventricular origin.
3.1	280	100	
3.20	278	109	
3.40	300	93	
4.0	300	104	
4.20	320	119	
4.40	273		Pure flutter developed over night, the rate falling to 232. The simultaneous fall of ventricular rate is exceptional.
5.0	297		
5.20	283		
5.45	256		
6.0	270		
Nov. 22 12 noon	232	58	
Nov. 23 10.0	252	63	The effects of quinidine pass off, but pure flutter is maintained.
4.0	252	63	
Nov. 24 10.30	258	67	
3.0	258	64½	The auricular rate rises to its stable level of about 258.
Nov. 28 10.0	256	64	
10.20	258	71	
10.25	259	66	The mechanism remaining unchanged and the auricular rate being constant for 5 days, further quinidine is given.
10.30	Quinidine 0.6 gr.		
10.50	259	68	
11.10	254	63½	Pure flutter continues, the ventricle responding 4:1, occ. 2:1. The auricular rate begins to fall slightly.
11.30	250	72	
11.50	234	93	
12.10	224	112	Pure flutter continues, the ventricle at first responding 2:1 and occasional 4:1; when the auricular rate falls to 226, pure 2:1 block is established and the ventricular rate rises. This fall of auricular rate under quinidine is ascribed purely to an effect on conduction.
12.30	222	111	
1.10	218	109	
1.30	218	109	
1.50	226	113	
2.10	224	112	
2.30	226	113	
2.50	225	106	
3.10	225	112½	
3.30	228	114	
3.50	227	113½	
Nov. 30 10.0	257	67	Recovery from quinidine next morning; the auricular rate rises and the ventricular rate falls. Pure flutter still maintained.
Dec. 2 10.0	266	60	
Dec. 13	Flutter persists as before.		Digitalis tincture drachms 20.
Dec. 13 to Jan. 2			
Jan. 2	484	57	Fibrillation of auricles.

*Case 2.* J. M. A man, aged 42. Admitted July the 2nd, 1921. No history of rheumatic fever. Cardiac symptoms for 6 years. Mitral stenosis and auricular fibrillation, the last known to have been present for 23 months. No signs of congestion. Heart not enlarged. Poor exercise tolerance.

Observations on this case will be found on Tables I and II.

*Case 3.* A. A. A man, aged 43. Admitted September the 12th, 1921. History of rheumatic fever at 15. Cardiac symptoms for 6 years. Mitral stenosis, pericardial adhesions and auricular fibrillation, the last known to have been present for 18 months, and probably present for 5 years. Signs of slight congestion present. Heart considerably enlarged. Poor exercise tolerance.

Observations on this case will be found in Tables I and II.

*Case 4.* W. A. A man, aged 54. Admitted September the 15th, 1921. No history of rheumatic fever. Cardiac symptoms for 5 years. Fibrillation of auricles known to have been present for 4 months. No signs of congestion. Heart moderately enlarged. Poor exercise tolerance.

Observations on this case will be found in Tables I and II.

*Case 5.* J. M. A man, aged 38. Admitted to hospital September the 12th, 1921. No history of rheumatic fever. Cardiac symptoms for  $2\frac{1}{2}$  years, fibrillation of auricles known to have been present for 4 months. No signs of congestion. Heart not enlarged. Poor exercise tolerance.

Observations on this case will be found in Tables I, III, IV and in Fig. 13.

*Case 6.* E. A. A man, aged 34. Admitted September the 26th, 1921. No history of rheumatic fever. Cardiac symptoms for 12 months. Mitral stenosis and auricular fibrillation, the last known to have been present for 4 months. Signs of congestion present. Heart moderately enlarged. Poor exercise tolerance.

Observations on this case will be found in Tables I, III and IV, and in Fig. 12.

*Case 7.* D. L. A man, aged 46. Admitted November the 9th, 1921. No history of rheumatic fever. Cardiac symptoms for  $6\frac{1}{2}$  years. Auricular fibrillation known to have been present for 5 months, and probably present for three years. No signs of congestion. Heart slightly but definitely enlarged. No valvular lesion. Very poor exercise tolerance.

Observations on this case will be found in Tables II, III and IV, and in Fig. 15.

*Case 8.* F. W. A man, aged 26. Admitted November the 10th, 1921. No history of rheumatic fever. Cardiac symptoms for  $6\frac{1}{2}$  years. Mitral stenosis and auricular fibrillation, the last known to have been present for 20 months, and probably present for 4 years. No signs of congestion. Heart considerably enlarged. Moderate exercise tolerance.

Observations on this case will be found in Tables II, III, IV and VIII, and in Figs. 6 and 16.

*Case 9.* E. P. A man, aged 29. Admitted November the 2nd, 1921. No history of rheumatic fever. Cardiac symptoms for  $2\frac{1}{2}$  years. Mitral stenosis and auricular fibrillation, the last known to have been present for 10 months. No signs of congestion. No definite signs of enlargement. Poor exercise tolerance.

An observation on this case will be found on page 244.

*Case 10.* J. N. A man, aged 34. Admitted December the 3rd, 1921. No history of rheumatic fever. Cardiac symptoms for nearly 3 years; fibrillation of auricles known to have been present for 4 months, and probably present for 11 months. No signs of congestion. Heart not enlarged. Fair exercise tolerance.

Observations on this case will be found in Table VIII, and in Figs. 3 and 18.

*Case 11.* H. S. A man, aged 40. Admitted August the 31st, 1921. No history of rheumatic fever. Cardiac symptoms for 2 years. Mitral stenosis and auricular fibrillation, the last known to have been present for 5 months. Signs of slight congestion present. Heart moderately enlarged. Poor exercise tolerance.

Observations on this case will be found in Tables III and IV, and in Fig. 11.

*Case 12.* T. C. A man, aged 52. Admitted August the 31st, 1921. No history of rheumatic fever. Cardiac symptoms for 2 years. Mitral stenosis and auricular fibrillation, the last known to have been present for 14 months. No signs of congestion. Heart moderately enlarged. Poor exercise tolerance. History of nephritis and bronchitis.

Observations on this case will be found in Tables III and IV, and in Figs. 2 and 5.

*Case 13.* H. P. A man, aged 30. Admitted December the 12th, 1921. No history of rheumatic fever. Cardiac symptoms for  $4\frac{1}{2}$  years. Mitral stenosis and auricular fibrillation, the last known to have been present for 12 months, and probably present for 3 years. No signs of congestion. Heart definitely enlarged. Poor exercise tolerance.

Observations on this case will be found in Tables III and IV, and in Fig. 14.



*Case 14.* F. R. A man, aged 59. Admitted January the 18th, 1921. No history of rheumatic fever. Cardiac symptoms for 1 year, fibrillation of auricles known to have been present for 3 weeks, and probably present for 6½ months. Signs of slight congestion. Heart moderately enlarged. Poor exercise tolerance.

Observations on this case will be found in Tables III and IV, and in Fig. 17.

*Case 15.* S. D. A man, aged 38. Admitted May the 5th, 1921. No history of rheumatic fever. Cardiac symptoms for 5½ years. Mitral stenosis and auricular fibrillation, the last known to have been present for 1½ years. Signs of congestion present. Heart considerably enlarged. Poor exercise tolerance.

Observations on this case will be found in Table III.

*Case 16.* C. B. A man, aged 34. Out-patient. Repeated history of rheumatic fever. Cardiac symptoms for 4 years. Mitral stenosis and pericardial adhesions and auricular fibrillation, the last known to have been present for 14 months, and probably present for 3 years. No signs of congestion. Heart moderately enlarged. Poor exercise tolerance.

Observations on this case will be found in Table III.

*Case 17.* F. F. A man, aged 45. Admitted April the 13th, 1921. No history of rheumatic fever. Cardiac symptoms for 2 years. Fibrillation of auricles known to have been present for 9 months. Signs of congestion. Heart moderately enlarged. Poor exercise tolerance.

Observations on this case will be found in Table III.

*Case 18.* A. H. A man, aged 38. Admitted July the 22nd, 1921. No history of rheumatic fever. Cardiac symptoms for 5½ years. Mitral stenosis and auricular fibrillation, the last known to have been present for 9 months, and probably present for 3½ years. No signs of congestion. Heart slightly enlarged. Good exercise tolerance.

Observations on this case will be found in Table III.

*Case 19.* J. C. A man, aged 37. Admitted April the 5th, 1921. No history of rheumatic fever. Cardiac symptoms for 5 years. Fibrillation of auricles known to have been present for 9 months. No signs of congestion. Heart not enlarged. Poor exercise tolerance.

Observations on this case will be found in Fig. 9.

*Case 20.* D. C. A man, aged 46. Admitted January the 1st, 1921. No history of rheumatic fever. Cardiac symptoms for 5½ years. Fibrillation of auricles known to have been present for 13 months, and probably present for 4½ years. No signs of congestion. Heart slightly enlarged. Poor exercise tolerance.

Observations on this case will be found in Fig. 8.

*Case 21.* H. H. A man, aged 30. Admitted October the 21st, 1921. No history of rheumatic fever or syphilis. Cardiac symptoms for 3½ years. No fainting attacks. Auricular fibrillation with a regular action of the ventricle; the usual rates of the ventricle were 40 to 48 per minute. This mechanism is known to have been present for 10 months, and has probably been present for 2 years. No valvular disease. No signs of congestion. Heart slightly enlarged. Good exercise tolerance.

Observations on this case will be found in Fig. 7.

On October the 31st, he was given 0.6 of a gramme of hydroquinidine.

Time.	Auricular rate.	Ventricular rate.	Remarks.
9.15	501	47	} Fibrillation of auricles and complete heart block.
9.30	492	44	
9.45	482	44	
10.0	512	41	
10.30	522	39	
10.40	Hydroquinidine 0.6 gr.		} Auricular action slows under hydroquinidine.
11.0	514	40	
11.20	520	38	
11.40	535	39	
12.0 noon	399	48	
12.35	342	44	} Normal auricular rhythm and complete block.
1.0	78	41	
1.20	74	39	

*Case 22.* W. C. A man, aged 49. Admitted January the 24th, 1922. Repeated history of rheumatic fever. Cardiac symptoms for 6 years. Mitral stenosis and auricular fibrillation, the last known to have been present for 3 weeks, and probably present for 2 years. No signs of congestion. Heart moderately enlarged. Poor exercise tolerance.

Observations on this case will be found in Fig. 19.

Case 23. R. S. A man, aged 41. Admitted January the 20th, 1922. History of rheumatic fever at 17. Cardiac symptoms for 7 years. Mitral stenosis and auricular fibrillation, the last known to have been present for 12 months. No signs of congestion. Heart slightly enlarged. Poor exercise tolerance.

Observations on this case are referred to on page 245.

Case 24. F. M. A man, aged 23. Admitted August the 9th, 1921. No history of rheumatic fever. Cardiac symptoms for 3½ years. Mitral stenosis and auricular fibrillation, the last known to have been present for 12 months. Signs of congestion present. Heart definitely enlarged. Poor exercise tolerance.

Observations on this case are to be found in Table VII, and in the following special protocol.

Date and time.	Auricular rate.	Ventricular rate.	Remarks.
Aug. 15 10.0	C. quinidine sulph. 0.4 gr.		Fibrillation, the auricular rate falling after quinidine.
10.1	490	82	
12 noon	407	78	
2.0	400	85	
4.0	423	85	
4.30	C. quinidine sulph. 0.4 gr.		Some recovery over night. Dosage increased. Auricular rate falls lower to 340, and ventricular rate now rises to 120. Impure flutter.
5.30	408	87	
Aug. 16 8.0	C. quinidine sulph. 0.4 gr.		
10.0	466	82	
12 noon	366	79	
12.1	C. quinidine sulph. 0.4 gr.		Impure flutter continues, the auricular rate remaining down.
2.0	400	87	
4.0	393	82	
4.1	C. quinidine sulph. 0.4 gr.		
6.0	346	120	
Aug. 17 8.0	C. quinidine sulph. 0.4 gr.		Pure flutter developed, the rate of the auricle jumping down to 222. The ventricle responding regularly 2:1.
10.0	347	80	
12 noon	303	75	
12.1	C. quinidine sulph. 0.4 gr.		
2.0	343	91	
4.0	313	78	The auricular rate falls to 200, and the ventricle assumes the same rate.
4.1	C. quinidine sulph. 0.4 gr.		
6.0	322	87	
Aug. 18 8.0	C. quinidine sulph. 0.4 gr.		
9.0	222	111	
10.20	225	112½	Quinidine having been stopped the auricular rate lifts a little and 2:1 ventricular response returns.
11.30	214	107½	
12 noon	210	105	
1.15	200	200	
1.30	202	202	
2.15	218	109	The auricular rate recovers further, and 2:1 responses are often mixed with 4:1 responses.
2.50	220	110	
3.0	222	111	
3.30	220	110	
4.30	232	116	
5.0	230	100	Tincture of digitalis was begun in doses of a drachm a day on the 20th; but the rates showed little change until the 24th. Total of 4 drachms given.
Aug. 19 10.0	246	102	
2.30	250	100	
4.0	254	127	
Aug. 20 10.0	260	130	
12 noon	256	128	Fibrillation of auricles. Note that the rate of oscillation is higher than originally.
Aug. 22 10.0	266	100	
12 noon	270	120	
2.0	270	100	
5.15	272	120	
Aug. 23 10.0	270	112	
4.0	272	100	
Aug. 24 10.0	573	74	
12 noon	580	58	
2.0	600	61	



Case 25. R. S. A man, aged 26. Admitted August the 16th, 1921. No history of rheumatic fever. Cardiac symptoms for 3 years. Mitral stenosis and auricular fibrillation, the last known to have been present for 1 month; probably present much longer. No signs of congestion. No definite signs of enlargement. Fair exercise tolerance.

The following protocol shows special features referred to in the text.

Date and time.	Auricular rate.	Ventricular rate.	Remarks.
Aug. 22 10.0	C. quinidine sulph. 0.4 gr.		
10.1	573	63	
12 noon	513	63	
1.0	C. quinidine sulph. 0.4 gr.		Fibrillation of auricles; auricular rate falling and ventricular rate rising under quinidine.
2.0	450	77	
4.0	C. quinidine sulph. 0.4 gr.		
4.1	430	77	
5.30	425	83	
Aug. 23 At 10.10, 12.0 and 4.0,	0.4 gr. C. quinidine sulph.		
10.30	470	61	
3.40	331	92	
Aug. 24 At 11.0 and 4.0,	0.4 gr. C. quinidine sulph.		
10.0	490	64	
12 noon	492	65	
2.0	402	77	Recovery each night and fall of auricular rate during the day in response to 3 doses of quinidine sulphate.
4.0	340	79	
5.15	387	80	
Aug. 25 At 11.0, 1.30, 4.0 and 8.0	C. quinidine sulph.		
10.0	473	66	
12 noon	480	61	
2.0	386	82	
4.0	342	81	
5.0	221	96	Abrupt fall of rate and establishment of pure flutter. 2:1 and occ. 4:1 response.
Aug. 26 At 4.0, 10.0, 2.0, 4.0, 8.0 and 12 mid.,	0.4 gr. sulphate.		
10.0	240	80	
2.0	235	83	Pure flutter continues without much change. Ventricle gives 3:1 or mixed response.
4.0	246	93	
5.0	230	90	
Aug. 27 At 4.0, 8.0, 2.0 and 6.0,	0.4 gr. sulphate.		
10.0	202	101	
12.0	218	78	Pure flutter continues.
Aug. 28 2.0	276	92	Pure flutter, auricular rate recovering from quinidine.
At 2.0, 5.0, 8.0 and 12 noon,	0.2 gr. sulphate.		
Aug. 29 At 4.0 a.m. and 12.30,	0.4 gr. sulphate.		
10.30	264	100	
12 noon	264	80	
2.0	272	90	Small doses of quinidine produce a little fall of auricular rate.
4.0	250	96	
5.0	264	96	
Aug. 30 10.0	278	85	
4.0	280	93	
Aug. 31 10.0	282	70½	Pure flutter persists. The auricular rate rises to 280 when quinidine is withdrawn and remains at this rate for days. The ventricle usually responding regularly to each 4th auricular beat.
12 noon	286	62	
Sept. 1 10.0	289	63	
2.0	288	72	
Sept. 2 10.0	280	70	
5.0	280	70	

Case 26. A. P. A man, aged 54. Admitted August the 5th, 1921. No history of rheumatic fever. Cardiac symptoms for 6½ years. Mitral stenosis and auricular fibrillation, the last known to have been present for 3½ years. No signs of congestion. Heart moderately enlarged. Fair exercise tolerance.

The following observations referred to in the text were made upon him.

Date and time.	Auricular rate.	Ventricular rate.	Remarks.
Aug. 5 to Aug. 11	Resting in bed.		
Aug. 12	A morning and evening dose of 0.2 gr. C. quinidine sulph.		
Aug. 15	10.0 423	60	
	10.0 C. quinidine sulph. 0.4 gr.		
	12 noon 335	61	
	1.30 C. quinidine sulph. 0.4 gr.		
	2.0 271	85	
	4.0 60	60	Normal rhythm.
Aug. 17	Normal rhythm with frequent extrasystoles. 0.4 C. quinidine sulphate given daily up to the 22nd.	One dose of and including	
Aug. 22	Fibrillation resumed and continued till September the 5th.		
Sept. 5	10.0 C. quinidine sulph. 0.4 gr.		
	10.30 410	68	
	11.15 263	80	
	12 noon 262	84	
	12.30 C. quinidine sulph. 0.4 gr.		
	12.40 264	98	
	1.10 274	98	
	1.40 284	90	
	2.10 272	80	
	2.30 269	75	
	2.50 280	74	
	3.10 288	84	
	3.30 57	57	Normal rhythm.
Sept. 14	Fibrillation resumed and continued till September the 21st		
Sept. 21	C. quinidine sulph. 0.4 gr., at 10.0 and 12.30.		
	3.30 70	70	Normal rhythm.
Sept. 28	10.0 452	65	Fibrillation of auricles.
	At 10.30 and 2.0, C. quinine sulph. 0.4 gr.		
	5.30 308	104	
	6.30 and 11.30, quinine sulph. 0.4 gr.		
Sept. 29	10.0 72	72	Normal rhythm.
Sept. 30	Fibrillation resumed and continued till October the 11th. During this interval 3½ drachms of tincture of digitalis administered.		
Oct. 11	10.0 C. quinidine sulph. 0.4 gr.		
	10.1 477	52	
	2.30 C. quinidine sulph. 0.4 gr.		
	2.31 318	56	
	4.30 63	63	Normal rhythm.

#### SUMMARY AND CHIEF CONCLUSIONS.

1. A clinical method of investigating the reactions of the fibrillating auricle is described.

2. Curves of rate (auricular and ventricular) responding to single test doses of quinidine are examined.

3. Given by the mouth there is no material difference between the reactions yielded by salts of quinidine having different solubility.

4. The reaction is related in its degree to the dose of quinidine given.

5. Quinidine has, weight for weight, 5 to 10 times as powerful an action as quinine.

6. Hydroquinidine, the chief impurity of commercial quinidine, has, weight for weight, a very slightly more powerful action than quinidine.

7. Digitalis when given in full doses increases the rate of the fibrillating auricle, as a rule.

8. The reaction of the fibrillating auricle to quinidine is adversely affected, though in minor degree, by full doses of digitalis. This adverse effect is more than counterbalanced by the control which digitalis exerts on the ventricular rate.

9. Atropine, as a rule, slows the fibrillating auricle, sometimes slowing it conspicuously.

10. In dogs, the dose of atropine, adequate to paralyse the vagi, amounts to from 0.05 to 0.1 milligramme per kilogram body weight. A paresis of the nerves is accompanied by doses half as great as these.

11. In man, 1/50 of a grain of atropine given hypodermically does not, as a rule, paralyse the vagus. To be certain of paralysis, as much as 1/10 of a grain is necessary.

12. Digitalis exerts its action on the ventricle in part directly and in part through the vagi. The proportion between these actions is probably variable in individual cases.

13. When digitalis quickens the fibrillating auricle or converts flutter into fibrillation, it does so by exerting a preponderating action through the vagus nerves.

14. The actions of atropine, quinidine and digitalis upon the fibrillating auricle are fully explained by the theory of circus movement.

15. Clinical evidence is brought forward to show that quinidine produces only a partial paralysis of the vagi, when it is used in therapeutic doses in cases of auricular fibrillation.

16. In the same circumstances quinidine is shown to produce a slight grade of A-V block clinically.

17. The reasons why the ventricle accelerates, when auricular fibrillation is treated by means of quinidine, is fully discussed on the basis of clinical observations. Paresis of the vagus and lowered auricular rate each plays its part, while block developed in the *A-V* tissues partly counteracts the effects of these.

18. It would seem that atropine is unlikely materially to aid the therapeutic reaction of a fibrillating auricle to quinidine.

19. Evidence is brought forward that an essential difference between clinical flutter and fibrillation is that, in the former, the gap between the crest and wake of the circulating wave is greater. The difference probably accounts for the slower and more regular beating of the fluttering as opposed to the fibrillating auricle.

20. The nature of abnormal ventricular beats, occurring under quinidine, is discussed; the evidence seems to point to their extrasystolic origin. The phenomenon is compared to that which occurs in digitalis coupling, and it is suggested that a common causation may, perhaps, be found in the similar influence which quinidine and digitalis exert on the refractory period, rendering possible a re-entry of the wave for one or more cycles.

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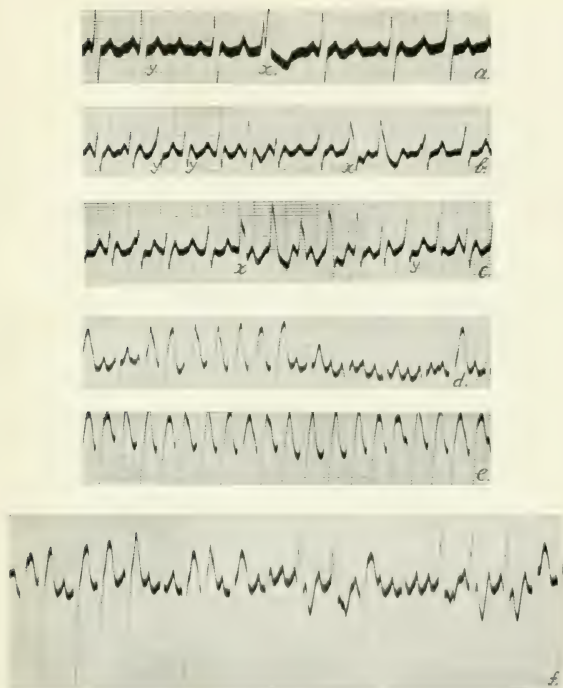


Fig. 20. A series of records taken, with chest leads, from patients during quinidine therapy. *a*. A curve taken by chest lead from a patient who had taken 3.6 grammes of quinidine sulphate in 24 days. *b*. A similar curve from another case after 1.6 of a gramme of quinidine sulphate had been taken in 11 days. *c*. A similar curve from the same case after 2.0 grammes of quinidine sulphate had been taken in 2 days. *d* and *e*. Similar curves from another case after 1.2 grammes pure quinidine base had been taken in 1 day. *f*. From the same case in which abnormal beats arising in both ventricles are shown, and in which beats of normal outline appear occasionally.





PAROXYSMAL VENTRICULAR FIBRILLATION WITH CARDIAC  
RECOVERY IN A CASE OF AURICULAR FIBRILLATION AND  
COMPLETE HEART-BLOCK WHILE UNDER QUINIDINE  
SULPHATE THERAPY.

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THE recorded instances of ventricular fibrillation in the human subject are few in number, due to the promptness with which death ensues when the condition becomes well established. Most of the records have been obtained at the time of death. The interpretation of the electrocardiographic record in the first published case by Hoffmann<sup>2</sup> obtained at the end of an attack of paroxysmal tachycardia has been questioned: it is said to represent a transition stage with impulses arising from several ventricular foci. Robinson<sup>3</sup> reports two cases of ventricular fibrillation, with electrocardiographic records obtained after the clinical death of the patients. In one of these cases (following death from poliomyelitis), the ventricular fibrillation was of brief duration and was followed by one abnormal ventricular complex. In the other case (following death from pneumonia) there was a brief period of ventricular fibrillation followed by slow ventricular rhythm for about one and one-half minutes. That but one of these records shows ventricular fibrillation is suggested by Lewis.<sup>4</sup> In a case of broncho-pneumonia at the time of death, Halsey<sup>1</sup> obtained electrocardiograms showing what has been considered as well established ventricular fibrillation. Robinson and Bredeck<sup>3</sup> report a case of ventricular fibrillation occurring during the last of three attacks of cardiac syncope, with cardiac recovery and death thirty hours later. Lewis also believes that this electrocardiogram represents "the last of those preliminary disturbances which precede full fibrillation" and "a less advanced grade of disorder than does that of Halsey."<sup>4</sup>

The observations here recorded were made over a period of a year, during which time there were several attacks of cardiac syncope, resembling Stokes-Adams syndrome, following the administration of quinidine sulphate. During some of these attacks electrocardiograms and polygraphic tracings were made. The electrocardiograms show different types of ventricular rhythm. Originally auricular fibrillation, complete heart-block and defective conduction in the ventricles\* were present. During the period of observation paroxysms of ventricular tachycardia were observed. Electrocardiograms were obtained resembling the curve of ventricular fibrillation as reported by Halsey. One record of very unusual type, which probably more nearly represents ventricular fibrillation than any other hitherto published, from the human subject was recorded. The patient recovered, and is now, nine months after these unusual attacks, in better health than at any time since he came under observation.

This patient had been under treatment with quinidine sulphate at the time when the cardiac syncope supervened, and its relation to this will be discussed later.

#### *Clinical summary.*

J. W. F. P., a clerk of 68 years, first came under observation in the outpatient department of the University of California Medical School on the 31st of May, 1921.

The onset of his complaint dated from about May, 1917, when he noticed gradually increasing palpitation, dyspnoea, cyanosis and œdema of the ankles. These symptoms continued for about three weeks, when orthopnea developed, and he consulted Dr. René Binc, of San Francisco, to whom we are indebted for the use of his excellent office records. When first examined by Dr. Binc, on May the 30th, 1917, the heart was enlarged to the left, the sounds were faint, the rate was about 40, the systolic blood pressure 150, and the diastolic pressure 100 mm. Hg: œdema of the ankles, marked cyanosis, moderate passive congestion of the lungs and ascites were present. His weight was 232 pounds. Digitalis and eliminative treatment were prescribed, and on July the 31st, 1917, he had improved, the heart being still enlarged: there were no murmurs, the rate was 96, and many extrasystoles were present: his weight was 200 pounds. During 1918 and 1919 he continued in much the same condition and was fairly well compensated for light activity. The heart rate varied between 80 and 96, with "numerous extrasystoles," and the systolic blood pressure ranged between 170 and 180, the diastolic from 90 to 100 mm. Hg. During this period the liver became palpable and gradually enlarged. He went back to his clerical work.

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\* There is a difference of opinion as to whether the curves obtained represent a left or right bundle-branch lesion. Experimentally similar curves are obtained by severing the left branch of the His bundle while clinically cases are reported where more extensive damage is found in the right heart.

There was another period of failure in November, 1920, with cyanosis, dyspnoea, abdominal distension, oedema and weakness. At this time the pulse was regular, the rate varying between 50 and 60; the blood pressure was 240 systolic and 90 diastolic; there was a blowing systolic murmur at apex and base. A note on December the 15th, 1920, stated that he was improved and the heart rate was 36.

On January the 5th, 1921, he had a dizzy spell in the street, but did not become unconscious. When next examined, the rate was 30 and the rhythm regular.

The patient came to the out-patient department on May the 31st, 1921, four years after the onset of his symptoms, complaining of oedema of the ankles and dyspnoea. He gave a history of scarlet fever in childhood, but had never had tonsillitis or rheumatism; he had a probable primary luetic lesion at 23 years, but there were no secondary manifestations. The results of examination were essentially as recorded above. The heart was enlarged, the rhythm regular, the rate 31 and the systolic blood pressure

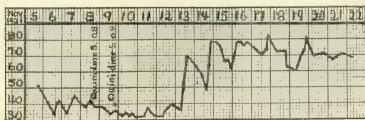


Fig. 1. Curve of radial pulse in case presented. The attacks of syncope occurred on November the 9th and 10th, but the pulse rate did not rise to the normal rate until November the 13th. The pulse has since varied from 70 to 90.

was 170 mm. and the diastolic 90 mm. Hg. The liver was enlarged and the ankles were conspicuously edematous. The urine contained a heavy cloud of albumen; the blood Wassermann was negative. The reflexes and pupils were normal. An electrocardiogram showed *auricular fibrillation, complete heart-block*, with a ventricular rate of 40 and defective ventricular conduction. Tincture of digitalis, minims XV, t.i.d., was prescribed over a period of 10 days. On June the 11th, 1921, a general and electrocardiographic examination showed his condition to be the same.

The patient was admitted to the medical ward on September the 12th, 1921, for observation, having had no medication for three months. At that time he felt well, except for slight dyspnoea and nocturia. There was extreme cyanosis, the heart was enlarged to right and left, and the apex beat was located in the 5th left interspace 13 cm. from the mid-sternal line: the sounds were muffled, apical and basal systolic murmurs were heard: the rhythm was regular and the rate 32: the systolic blood pressure was

220 mm. and the diastolic 75 mm. Hg. The rounded liver edge was easily felt 3 cm. below the costal margin: the pressure of feeling it evoked pain. There was moderate generalised peripheral arteriosclerosis. The urine contained a faint trace of albumen. The blood Wassermann was again negative. An electrocardiographic tracing showed no essential change.

It was decided to try the effect of quinidine sulphate in this case of complete heart block associated with auricular fibrillation. If the auricles and ventricles were affected separately it was thought that this would be brought out by study under administration of the drug. On September the 13th a single dose of quinidine sulphate 0.4 of a gramme was given. This was followed shortly by a brief period of bigeminal pulse without subjective symptoms. The attack lasted only a few minutes and disappeared before an electrocardiogram could be obtained. It was probably due to abnormal ventricular beats. Another dose of 0.4 of a gramme was given on September the 14th, without noticeable effect. On September the 15th and 16th, 0.4 of a gramme was given four and three times respectively. On September the 16th, after having taken a total of 3.6 grammes over a period of four days, the patient had an attack of syncope, lasting a few seconds. An electrocardiogram taken shortly afterwards showed bigeminal rhythm with abnormal ventricular complexes of extremely wide deflection following each regular beat. On September the 17th the abnormal ventricular beats had ceased and the ventricular rhythm returned, the rate varying between 30 and 40. No more quinidine was given at this time and the patient was discharged on September the 18th, showing no ill effects.

He was seen again on October the 20th, 1921. The general condition was somewhat improved and the heart findings were essentially the same as when he entered the hospital, except that the rhythm was very irregular with a slight pulse deficit, and the ventricular rate varied from 40 to 70. An electrocardiogram showed auricular fibrillation, ventricular rhythm irregular, but with complexes of the type noted when first observed, and a rate of 45 to 70. There was evidence of a left bundle branch lesion. Quinidine was prescribed and the dosage varied from 0.2 to 0.6 of a gramme daily for a period of two weeks. He was seen frequently during this time. The pulse varied from 38 to 80 and he felt unusually well.

On November the 5th, 1921, the patient was again admitted to the hospital for further observation and treatment. The physical examination showed no essential change, the heart rhythm was absolutely irregular, the rate at rest being about 48, and after exertion about 68.

Another course of quinidine was instituted, and on November the 8th four doses (0.2 of a gramme) of the sulphate were given without effect. On November the 9th a similar dose was given at 8 and 10, 12, and at 2 o'clock during the day. Shortly after the last dose the patient was taken to the electrocardiograph room. He returned feeling well until about 3 p.m. when, while walking about his room, he suddenly became faint and

fell to the floor, where he was seen a moment later lying unconscious, very cyanotic and taking an occasional gasping breath. The pulse was regular and weak, the rate being about 40. The cyanosis quickly disappeared: he developed Cheyne-Stokes breathing and consciousness gradually returned. The pulse rate increased to 60 and became irregular again. Within fifteen minutes his condition was as usual, except for some mental confusion. During the attack he lost a small amount of urine.

About twenty minutes later he announced that another attack was coming on and began to stare straight in front of him. His pulse could not be felt: he stopped breathing and lost consciousness almost instantaneously.

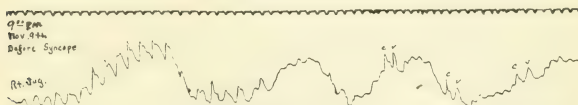


Fig. 2. November the 9th, 1921, 9 p.m.. Polygraphic tracing\* of the jugular pulse showing one of the attacks of rapid forceful beating of the heart, not associated with syncope. Rate 200. Time-marker for polygraphic tracings in fifths of a second.

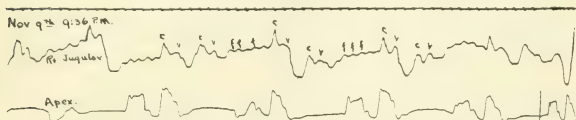


Fig. 3. November the 9th, 1921, 9.36 p.m.. Polygraphic tracing\* showing bigeminal rhythm about a half-hour after an attack of syncope.

\* Polygraph tracings are by Stafford L. Warren, senior student, who was of great assistance in the technical details.

His colour grew transiently pale, then very cyanotic, and no radial pulse could be felt or heart sounds heard for several seconds. The heart was then massaged with the fingers pushed deep under the rib margin, and while this was being done a quivering of the heart could be felt but no pulsations. Within a minute or two, apex and radial beats could again be felt, at first slow, feeble and regular: as they gained in strength the rate became more rapid and at times the rhythm was irregular. This was interspersed with short periods of very rapid heart beats, about 140 or more per minute, and fairly regular. Consciousness and colour returned as in the previous attack.

A third attack of syncope occurred about thirty minutes later (at 5.15 p.m.) and the heart sounds could not be heard for thirty seconds. The quivering of the heart could again be felt. Polygraphic tracings were

obtained. A similar but shorter attack occurred at 7.45 in the evening, and the short periods of tachycardia were again present preceding and during recovery from it. Electrocardiograms and polygraph tracings were made. The fifth attack, which occurred at 9.08 p.m., was likewise short. Records were again obtained. No more attacks occurred during the night and the patient slept at intervals, in which Cheyne-Stokes breathing was marked. The pulse rate varied between 40 and 55 through the night, at times regular with an occasional extrasystole, at others absolutely irregular. The sixth and last attack, which was very short and mild, occurred at 9 a.m. on November the 10th.

Thereafter he improved gradually up to the day of discharge, November the 22nd, when he was walking about and in about the same condition as on entry. The sensorium remained clouded for several days after the attacks of syncope, but slowly cleared up. The pulse rate in the meantime had been around 80 and absolutely irregular, the systolic blood pressure varying from 170 to 210 mm. with the diastolic pressure remaining at 90 mm. Hg. For about two months after discharge the patient was examined and electrocardiographic tracings made at weekly intervals. During this time the circulation remained essentially the same as at the time of discharge. He has since been seen at less frequent intervals, but on his most recent visit no change was noted in his condition. Since discharge he has had one transient attack of faintness, but nothing approaching those observed in the hospital. The pulse rate has varied from 70 to 90 for the past six months.

### *Discussion.*

As far as we are aware, there have been no reports of the action of quinidine on complete heart-block associated with auricular fibrillation. In our case there was complete block until the first quinidine was administered. Thereafter the ventricular rate varied from 30 to 70, but usually was regular with a rate of 40 to 45 per minute. There was evidence of slowing of the auricular rate. But our case is presented mainly with the hope that it may be of value in helping to explain attacks of syncope such as are known occasionally to occur under quinidine.

Coupling of the ventricular beats was noted, and in addition there were several series of rapid ventricular beats with a rate varying from 180 to 225 per minute. Several of the latter paroxysms are shown in Figs. 8 and 10; they had an average duration of seven to ten seconds and, as the curves show, were ventricular in origin. These curves are not curves of ventricular fibrillation, for while they were taken the patient retained consciousness, and a forceful apex-beat and a bounding rapid pulse were noted simultaneously. A venous curve of the jugular pulse during a series of abnormal ventricular beats is shown in Fig. 2. Types of abnormal ventricular beats occurring between such periods of tachycardia are shown in Fig. 11. Fig. 12, however, represents a more irregular form, and the rate is about 120 per minute;

the curve closely resembles that described by Halsey. This curve was obtained during an attack of syncope with apparent asystole at the heart, which further supports the view of its nature: it must be regarded as fibrillation of the ventricle, or a condition closely allied to it. But if Fig. 12 is a curve of fully developed ventricular fibrillation, we are at a loss to explain Fig. 9, which is a portion of a curve obtained while the patient was in deep syncope, and during which time no sound could be heard at the heart, and the pulse was imperceptible. Three of such curves were noted on the galvanometer string, all occurring during the same attack of syncope. We believe that the latter curve (Fig. 9) shows a more advanced process than Fig. 12, and more nearly represents ventricular fibrillation than any records of the human subject hitherto published.

The observations recorded suggest a danger of quinidine therapy. Other authors have described tachycardias or coupling of ventricular beats under quinidine. Levy<sup>3</sup> describes such occurrences and warns us against the further administration of the drug when such findings are noted. This author mentions four cases, reported in past records, where cessation of the heart and respiration with syncope were noted. Fortunately all of these patients recovered. It is possible if not probable that ventricular fibrillation was present in these cases as in ours.

The observations in our case indicate that the unfavourable action of the drug does not always depend on the precise dosage. It will be noticed that on September the 13th, 1921, a single dose of 0.4 of a gramme was followed by a bigeminal pulse for a brief period. On September the 14th a dose of 0.4 of a gramme was without adverse effect. On September the 15th 0.4 of a gramme was given four times, and on September the 16th 0.4 of a gramme three times. After the last dose there was a brief period of syncope followed by a bigeminal pulse for a few hours. From October the 20th to November the 3rd the patient received from 0.2 to 0.6 of a gramme daily without ill effect. No further quinidine was given until November the 8th and 9th, when 0.2 of a gramme was administered four times in each day. After the last dose, on November the 9th, the attacks of syncope developed and the curves described were obtained.

The manner in which quinidine may lead to fibrillation of the ventricles remains to be discussed briefly. Extensive experimental and clinical studies with quinidine are throwing a new light on the nature of fibrillation of the auricles. Quinidine is known to bring fibrillation of the auricles to an end in many cases; and this action is ascribed by Lewis and his co-workers<sup>5,6</sup> to the power of quinidine to prolong the refractory period of the auricular muscle. Although this action of bringing fibrillation of the auricles to an end is clearly established, our own case definitely suggests that quinidine may in certain circumstances induce fibrillation. Are these two conclusions necessarily incompatible? It must be acknowledged that the manner in which quinidine may produce fibrillation of the ventricles is not fully understood. The underlying question has been briefly discussed by Lewis and



his co-workers,<sup>6</sup> who suggest that ventricular extrasystoles and tachycardia occurring as a result of quinidine administration may be due to change in the refractory period, whereby re-entry of the excitation wave upon the path it has already travelled is brought about. According to these writers, when fibrillation prevails, a sufficient lengthening of the refractory period, by preventing re-entry, will bring the underlying circus movement to an end. They hold, however, that a change in the length or conduction of the refractory period from normal may be a chief factor in inducing circus movement and state that a remedy such as quinidine, which tends to bring auricular fibrillation to an end, is not necessarily one which, given in smaller doses, tends to ward off fibrillation, but that the contrary may be the case.

### CONCLUSIONS.

1. A case of auricular fibrillation and complete heart-block is reported in which coupling of the ventricular beats, ventricular tachycardia and ventricular fibrillation occurred while under treatment with quinidine sulphate.

2. The periods of ventricular tachycardia suggest a circus movement in the ventricle.

3. A curve is shown which is unlike any heretofore published from the human subject, and which probably represents true ventricular fibrillation.

4. One of the dangers of quinidine therapy is emphasised.

5. This case of recovery from ventricular fibrillation is the longest on record, the patient being alive nine months after the attack was observed.

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- <sup>7</sup> ROBINSON, G. C. "A Study with the Electrocardiograph of the Mode of Death of the Human Heart." *Journ. exper. med.*, 1912, XVI, 291-302.
- <sup>8</sup> ROBINSON, G. C. and BREDECK, J. F. "Ventricular Fibrillation in Man with Cardiac Recovery." *Archiv. intern. med.*, 1917, XX, 725-738.



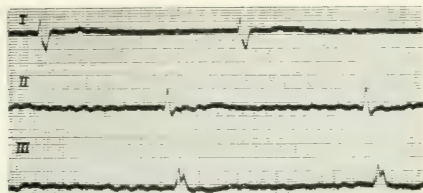


Fig. 4. Electrocardiogram, June the 1st, 1921, after a long course of digitalis and showing no change from original record. Complete heart-block, auricular flutter, and indications of a block in the left branch of the bundle. Traces and all subsequent curves are standardized so that deflections of 1 mm represent 0.1 mV. Time marker indicates twenty beats of a minute.

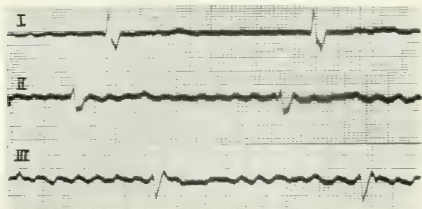


Fig. 5. September the 17th, 1921. Re-entry to case of the 1st following withdrawal of quinidine. On September the 16th the patient was given 1.2 grams of cinchonidine sulphate in three doses. After the last dose a brief attack of syncope occurred and the pulse showed a bigeminal rhythm. Curves show ventricular complexes of extremely wide deflection following each regular ventricular complex. In this record the curve in Lead III shows a slowing of the auricular rate and an altered ventricular complex.

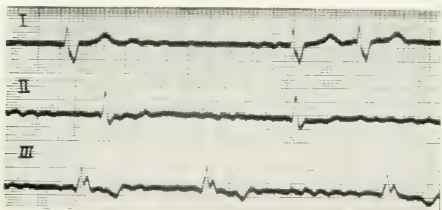


Fig. 6. November the 8th, 1921, 11.30 a.m. Record made on re-entry to hospital. The patient had taken quinidine 0.2 g. at intervals of four hours every day at home under observation during the previous two weeks. No untoward symptoms. Some irregularity of rhythm.



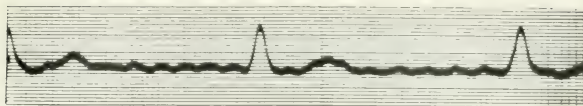


Fig. 7. November the 9th, 1921. Record made at 3 p.m. just before attacks of syncope began. Anterior and posterior chest lead. Quinidine sulphate 0.2 g. at 1, 3, 6 and 9 p.m. on November the 8th, and 0.2 g. at 1, 3, 6 and 9 p.m. on November the 9th.

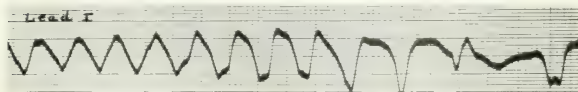


Fig. 8. November the 9th, 1921, 7.43 p.m.. Record made just before fourth attack of syncope at 7.45 p.m.. Free end and about half of this curve is shown. The patient was not in syncope when the record was obtained. A similar curve was obtained at 7.49 p.m.

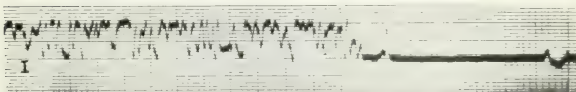


Fig. 9. November the 9th, 1921, 7.54 p.m.. Record obtained at one of three similar curves noted on galvanometer string. About half of the curve and its end is shown. Each period was of about equal duration. The patient was in syncope. The pulse was imperceptible. Note the very rapid irregular oscillations followed by an immense complex and at the extreme end of the curve a complex similar to those observed elsewhere in Lead *I*.

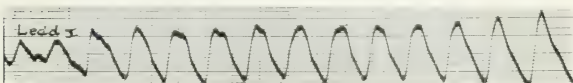


Fig. 10. November the 9th, 1921, 7.59 p.m.. Record showing another series of rapid deflections similar to curves in Fig. 8. The beginning and about half of this curve is shown. No similar curve could be produced by moving the extremities, feeling the pulse, listening to heart, or causing the patient to breathe deeply, swallow, or cough.



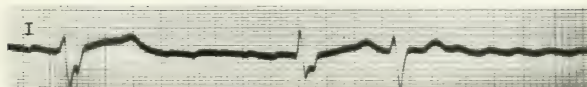


FIG. 11. November the 9th, 1921, 8.37 p.m. Record obtained just after a series of rapid deflections, not shown in trace. Note the varying shape of the ventricular complexes.

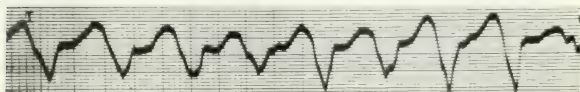


FIG. 12. November the 9th, 1921, 9.08 p.m. Record obtained during a period of rapid deflections lasting about a minute while the patient was in an attack of syncope of three minutes' duration. Polygraph tracings from the apex showed no movement of the heart from 9.08 to 9.09 p.m. Following this attack the heart resumed a regular rhythm, rate 45. No further attacks of syncope and no irregularities were noted on the galvanometer string up to 10 p.m., when observations were discontinued. This curve resembles those shown by Hulse's ventricular fibrillation.

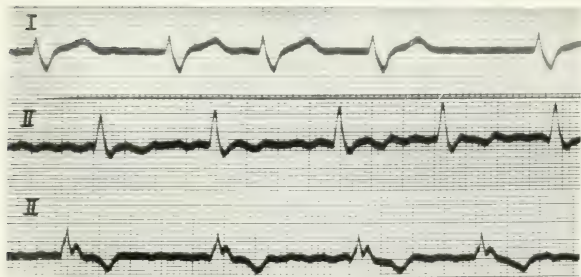


FIG. 13. March the 20th, 1922. Record obtained four months after attacks of syncope. Subsequent curves have shown no essential change.



## POST-MORTEM NOTES OF DR. J. H. STARLING'S CASE OF HEART-BLOCK.

By THOMAS LEWIS.\*

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In the last volume of this Journal, Dr. J. H. Starling reported a case of heart-block. When this patient first came under observation he displayed transient attacks of block. Usually the heart's rhythm was normal, but from time to time a series of syncopeal attacks occurred, and records of these attacks, taken by Dr. Starling, showed sudden cessation of the ventricular beat, the auricle continuing to contract. These attacks were shown to be related to vagal activity, being provoked by the act of swallowing and being abolished temporarily by atropine. A series of attacks occurred for the last time, and these were recorded, on May the 30th, 1919. On June the 28th and July the 31st, 1919, on January the 8th, August the 12th and November the 11th, 1920, complete block was recorded, the ventricular rate varying between 38 and 48 beats per minute. The previous account of this patient brings the history of the case to the last date.

Dr. Starling now writes that the patient was seen in January and June, 1921, and that the condition of the heart's rhythm was then unchanged. He was free from symptoms. "The harvest in this year commenced early, and he was doing his full day's work. On August the 3rd, 1921, he went out as usual to work, having made no complaint of feeling in any way different, and was found dead in the harvest field the same afternoon. Dr. Owens, of Long Stratton, kindly notified me of this event, and with some difficulty I was permitted to remove the heart from the body, but no further examination was allowed."

Dr. Starling forwarded the heart to me for examination.

*Appearance of the heart.* The heart, when emptied and with the vessels cut short, weighs 540 grammes. The epicardium is thickened slightly in places. The right auricle is dilated, the right ventricle is dilated and hypertrophied. The edges of the pulmonary valves are thickened; the tricuspid valve is normal. The left auricle is a little dilated and its endocardium irregularly thickened. The left ventricle is dilated and hypertrophied equally with the right chamber. There is a slight degree

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\* Observations undertaken on behalf of the Medical Research Council.

of thickening at the edge of the mitral segments, and a few small yellowish deposits in the flaps of the valve; otherwise the valve is normal. The aortic valves are a good deal thickened at their edges by fibrous tissue and small masses of calcareous tissue. The right and left anterior cusps, from which the corresponding and dilated coronary arteries spring, are thrown into one, the original line of sub-division being visible as a ridge in the sinuses of Valsalva. Below the junction of the posterior segment with its neighbour, the conjoined cusp, a tumour projects into the cavity of the ventricle. The tumour is rigid and finely nodular, and from its colour and consistence evidently contains calcareous matter. The mass is triangular in shape, the point projecting upwards and being firmly fixed to what was originally the right anterior cusp (see Fig. 1). The surface of the mass is glistening except over the summits of the small nodules of calcareous tissue: here the surface is rougher, but the calcareous tissue is not exposed to the blood stream. Below and behind this tumour the endocardium is densely thickened over a small area. The calcareous mass lies on the course of the left division of the bundle, the visible root of which can be traced into it from below. This mass does not project through the septum into the right ventricle. A few small fibro-calcareous patches are seen on the right or posterior papillary muscle. The base of the aorta is slightly atheromatous, more especially in and around the sinuses of Valsalva. The coronary vessels and their branches are dilated and atheromatous throughout their courses.

### *Histology.*

A block of tissue, including the coronary sinus and septal flap of the tricuspid valve, on the right side, the nodule of calcareous tissue and corresponding aortic cusps on the left side, was excised. The calcified tissue was decalcified after hardening in formalin, and the whole embedded in celloidin and cut in horizontal serial sections from above downwards.

The auriculo-nodal junction is normal. The auriculo-ventricular node, which consists of very many interlacing fibres, loosely embedded in fat, is normal. The first part of the bundle consists of densely packed fine parallel muscular fibres and is normal. The connective tissue surrounding the first part of the bundle is sparsely invaded by lymphocytes. The veins in the node and bordering the node are unusually capacious. The first part of the bundle runs horizontally, in its second half it bends downwards, and, as it bends, it becomes flattened from side to side, and is a little more fibrous than it should be; there are also small collections of lymphocytes in its substance. Shortly after the bend, a space develops between the bundle and the fibrous septum: this space is unlined and is crossed by irregular connective tissue strands. The bundle is now approaching the aortic valve cusps and lies more to the left than is usual, being, in fact, closer to the cavity of the left than to that of the right ventricle: the septum is here densely



thickened by fibrous tissue in which are large unfilled spaces. A little later the bundle is level with the calcareous node shown in Fig. 1. This node consists of a mass of calcareous material broken into rounded masses by fibrous septa, the whole being enclosed in a thick fibrous capsule. At the level of the attachment of the aortic cusps, this calcareous mass lies on a fibrous base, the mass itself being entirely outside the limits of the septal musculature: but when lower sections are examined it is seen to penetrate more and more into the septum until it comes to occupy an almost central position still distorting the endocardium of the left ventricle and approaching closely to that of the right ventricle. When the bundle reaches this central mass it divides, and here it is heavily damaged, the capsule of the nodule being in contact with the bundle division. The bundle division is invaded by many fibrous strands from this capsule, and, like the capsule, is densely infiltrated with lymphocytes. The left division of the bundle is traced in the capsule of the nodule, pursuing its course for a short distance on its endocardial surface, where it is speedily replaced by fibrous tissue and can no longer be followed. Remnants of the right division are traced along the posterior and upper surface of the nodule for a short distance: it is rapidly incorporated and lost in the fibrous capsule. The whole of this region of the septum is fibrous and infiltrated.

*Interpretation.* There is no material interference with A-V node or A-V bundle over the first half of its course. A calcareous deposit densely covered in and divided by fibrous strands has its seat in the septum just in front and below the bundle division. It forms a saddle over which the bundle divides; the division is in close contact with the capsule of this nodule, and shows evidence of a chronic inflammatory process by which it is heavily invaded: the two bundle branches have their brief course in this fibrous capsule, in which all trace of them is speedily lost, remnants of the left branch continuing for a little way in the fibrous tissue beneath the left septal endocardium. There appears therefore to be a complete breach in the conducting tissues, which, so it is judged, must have been destroyed for a period of at least many weeks or months. The calcareous nodule appears to have developed centrally and to have expanded towards the left ventricle, dragging the bundle across with it and distorting it.

#### COMMENT.

This case presents points of unusual pathological interest. Some few years ago I reported<sup>1</sup> a case in which attacks of a similar kind occurred, namely, attacks of sudden cessation of the ventricular beat, the auricular contractions continuing. As in the present case, during the intervals between attacks the man was well and the mechanism of the heart was quite normal. Eventually the first patient developed complete block and died of it.

In these features, therefore, the case resembles that of Dr. Starling; but his case differs from it in an important respect; whereas my own case failed to react to atropine, his case did react, and clear evidences of a relation between the attacks and the vagus nerve were produced. Nevertheless, despite this preliminary evidence of vagal involvement, the man developed complete block and died of it, presenting post-mortem a complete and old-standing lesion of the conducting tract. This illustration warns us that in cases of transient block, even though clear evidence is forthcoming that the vagus is immediately responsible for the attacks of heart-block, it is still unjustifiable to conclude that an abnormal vagal action is primarily or wholly responsible for the patient's symptoms. In the present case the most reasonable view appears to be that owing to disease of the junctional tissues, natural vagal impulses were from time to time associated with conspicuously exaggerated reactions.

The second point of interest is the lesion itself. Through the kindness of Dr. H. G. Butterfield I have had the opportunity of examining another case in which a very similar lesion existed. It consisted of a rounded nodule of fibro-calcareous tissue, about a centimetre in diameter and projecting into the left ventricle from the septum in precisely the same situation as the lower part of the nodule here described. The lesion in his patient was not, however, quite so simple as that of Dr. Starling's case. The calcareous node joined a calcareous bar which was continued backwards in the septum at a slightly lower level as far as the aortic flap of the mitral valve. Dr. Butterfield's specimen was taken from a case of complete and chronic heart block, but his sections failed to show an actual breach in the continuity of the bundle, which was but little invaded by actual disease. I call to mind a report\* of a third case in which the lesion was similar to that described in the present note and occupied an identical position, projection into the cavity of the left ventricle. It is suggested that lesions of this kind may be consequent upon disease of a particular branch of a septal artery, and that it might be wise, when a further opportunity presents itself, to study in such a specimen the vascular supply of the septum by the method of injection.

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STARLING. *Heart*, 1921, VIII, 31.

\* A published report to which I am no longer able to find the reference.



Fig. 1.



COMPARISON OF THE ACTION OF QUINIDINE WITH OTHER  
CINCHONA ALKALOIDS IN AURICULAR FIBRILLATION.\*

By R. T. GRANT and C. C. ILIESCU.

(*University College Hospital Medical School.*)

IN this article further observations on the action of the cinchona alkaloids upon the hearts of patients suffering from auricular fibrillation are described. Several of these alkaloids have been investigated experimentally and clinically by other workers. Santesson,<sup>7</sup> in experiments on rabbits and frogs estimated the minimal concentration of cinchonine, quinidine, quinine and cinchonidine, required in a perfusing fluid to bring the ventricle to a standstill and found that while cinchonine and quinidine were of equal potency, the concentration required by the last three alkaloids were in the proportions 1, 2 and 5. He noticed also that the relative potency of the four alkaloids is similarly ordered when lowering of the ventricular rate is taken as the measure. Langlois,<sup>5</sup> experimenting on different mammals, described cinchonidine as being less active in producing clonic spasms than cinchonine. Using the tortoise's ventricle, Fredericq<sup>1</sup> found that the levorotatory alkaloids, quinine and cinchonidine were more toxic than the dextrorotatory alkaloids cinchonine and quinidine, the equal toxic effects being produced by solutions of the drugs in the order, stated in this sentence, in the strengths per 1,000 of 2.5, 4, 5, 10. It is to be pointed out that the foregoing observations are related only indirectly to those of the present communication, which deals solely with the potency of the several alkaloids to reduce the rate of the fibrillating auricle. From this standpoint von Frey's observations are of more significance. Frey,<sup>2</sup> in treating auricular fibrillation, found that cinchonine had no appreciable effect, and stated that the most active of the alkaloids is quinidine.

*Preparations used.* The actions of four alkaloids are compared, namely, those of quinidine, cinchonidine, cinchonine and quinine. As before,<sup>6</sup> we are indebted to Messrs. Howard and Sons, of Ilford, for these drugs. The

\* Working on behalf of the Medical Research Council.

physical properties and degrees of purity of the preparations as supplied are given below in Table 1, information for which we are indebted to Drs. Blagden and Chick.

TABLE 1.

	Specific rotation.*	Melting point.	Impurities.†
Quinidine .. ..	- 323° 45'	172.3°C.	Less than 0.5% hydroquinidine.
Quinine .. ..	- 265° 0'	172.7°C.	Less than 0.5% cinchonidine.
Cinchonidine .. ..	- 173° 15'	211.0°C.	Less than 0.5% quinine.
Cinchonine .. ..	+ 255° 37'	264.0°C.	Less than 0.5% hydrocinchonine.

\* 2.0 grammes anhydrous base dissolved in 5 c.c. HCl of specific gravity 1.16, and made up to 100 c.c. with water at 17° C.

† The quantities of impurity here stated are approximate.

*Methods of testing the alkaloids clinically.* The method used was the same as that described in a previous paper,<sup>6</sup> namely, the administration of single test doses of the drugs to each of a series of patients, under conditions kept so far as possible uniform. Briefly the routine was as follows. Before the administration of the alkaloids the patients were left at rest for about a week or when they had been under digitalis up to the time of admission this period was increased to ten days or more. At the end of this time a preliminary dose of the alkaloid to be tested was given, usually 0.2 of a gramme, in order to ascertain the patient's tolerance for the drug. Forty-eight hours were allowed to elapse between this preliminary dose and the actual test dose. On the morning of the test dose the patients were brought to the laboratory at 9.15 a.m., having had their usual breakfast at 6 a.m. and bread and milk at 8.30 a.m., and after lying down at rest till 10 a.m. were connected with the galvanometer by direct chest leads and records were taken at intervals of ten minutes. At 11 a.m. the test dose was administered and records were taken every twenty minutes till 4 p.m.. The patients remained lying down throughout the observation, with the exception that they were allowed up for lunch between 1 and 1.15 p.m.. The rates charted are the average reading from the strips of curve. In the case of the auricular rate the time occupied by 10 oscillations in each of three strips of curve is averaged and the rate per minute calculated. The ventricular rate in beats per minute is calculated from the average of the number of ventricular cycles occurring in 10 seconds in each of the three strips.

*The form and time relation of the reactions.* Each of the four drugs gives the same type of reaction, with, however, variations in intensity and time relations. The reaction is the same as that previously described, namely, a fall of auricular rate followed by a gradual return towards the original level and at the same time a rise of ventricular rate also followed by a gradual return towards and to their original level.

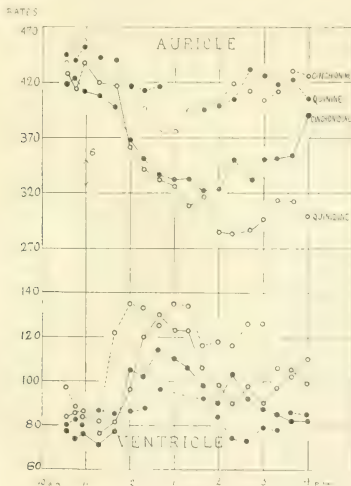


Fig. 1. Case 1. A chart comparing the effects on the auricular and ventricular rates of equal test doses of quinidine, cinchonidine, cinchonine and quinine, given in single doses of 0.6 of a gramme on the 8th, 13th, 31st of March, and the 4th of April, respectively.

#### *Comparison of the reactions of the allied alkaloids.*

Complete charts of two of the cases (Figs. 1 and 2) are shown to illustrate the variations in intensity and time relation of the reactions to each of the four drugs.

In Fig. 1 the test dose was constantly 0.6 of a gramme. Under *quinidine* the auricular rate before the administration of the drug was about 127 oscillations per minute. In 20 minutes the rate commenced to fall and

continued falling for a total of 3 hours, when it reached the minimal point at 283 per minute. This low level was maintained for about an hour, and thereafter the rate rose slowly and at the end of the observation (4 p.m.) had risen to 300. The difference between the initial rate of oscillation and the minimal point was 144. The initial ventricular rate averaged 85 beats per minute. After 20 minutes this had fallen to 76. Twenty minutes later

TABLE II.

*Comparison of quinidine, cinchonidine, cinchonine and quinine in seven cases.*

Case	Date.	Alkaloid.	Dose in grms.	Auricular rate.			Ventricular rate.	
				Before.	After.		Before.	After.
1.	March 8 ..	Quinidine ..	0.6	427	283*	296†	85	130
	.. 13 ..	Cinchonidine ..	0.6	418	320	350	76	114
	.. 31 ..	Cinchonine ..	0.6	450	372	402	88	135
	April 4 ..	Quinine ..	0.6	444	394	426	81	96
2.	March 13 ..	Quinidine ..	0.6	520	320	322	79	124
	.. 20 ..	Cinchonidine ..	0.6	511	356	396	81	118
	.. 27 ..	Cinchonine ..	0.6	510	400	430	79	140
	.. 31 ..	Quinine ..	0.6	510	372	436	73	90
3.	April 3 ..	Quinidine ..	0.4	623	390	470	64	70
	.. 6 ..	Cinchonidine ..	0.4	604	444	495	58	79
	.. 10 ..	Cinchonine ..	0.4	618	460	525	60	103
	.. 13 ..	Quinine ..	0.4	604	500	560	56	60
4.	April 3 ..	Quinidine ..	0.4	497	384	410	91	128
	.. 6 ..	Cinchonidine ..	0.4	501	380	428	85	126
	.. 10 ..	Cinchonine ..	0.4	502	406	470	86	134
	.. 13 ..	Quinine ..	0.4	518	440	470	89	83
5.	June 6 ..	Quinidine ..	0.4	472	324	360	80	120
	.. 13 ..	Cinchonidine ..	0.4	471	362	425	79	120
	.. 16 ..	Cinchonine ..	0.4	474	352	440	79	132
	.. 20 ..	Quinine ..	0.4	463	398	435	69	87
6.	June 6 ..	Quinidine ..	0.4	472	290	330	83	115
	.. 13 ..	Cinchonidine ..	0.4	474	318	345	69	116
	.. 16 ..	Cinchonine ..	0.4	469	335	385	77	129
	.. 20 ..	Quinine ..	0.4	472	358	392	83	110
7.	June 6 ..	Quinidine ..	0.4	438	310	340	77	95
	.. 13 ..	Cinchonidine ..	0.4	437	352	365	77	113
	.. 16 ..	Cinchonine ..	0.4	441	370	380	76	116
	.. 20 ..	Quinine ..	0.4	446	388	410	78	84

\* Minimal point of initial fall.

† About 4 hours after dose.

the rate rose to 81 and this rise continued to 12.40 p.m., when the maximal rate of 130 beats per minute was reached—a rise over the initial rate of 45 beats per minute.

Under *cinchonidine*, given 5 days later, the auricular rate in the same patient fell from 418 to 320 in three hours, a fall of 98 beats. The ventricular rate fell from an initial level of 76 to 71 in 20 minutes and thereafter rose



to the maximal rate of 114 at 12.40 p.m.. This was followed by a gradual return. The maximal rise was 38 beats over the initial level.

Under *cinchonine*, given 18 days after the administration of cinchonidine, the auricular rate fell from 450 to 372 in 2 hours and 40 minutes, a fall of only 78 oscillations per minute. The ventricular rate, however, showed a conspicuous rise. The initial level was 88; the administration of the test dose was followed by a slight fall as is usual and then the rate rose sharply to 135 at 12 noon, a rise from the initial level of 47 beats per minute.

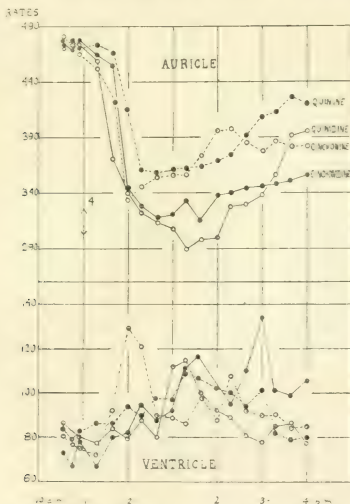


Fig. 2. Case 6. A chart comparing the effects on auricular and ventricular rate of equal test doses of quinine, cinchonidine, cinchonine and quinaidine given in single doses of 0.4 of a gramme on the 6th, 13th, 16th and 20th of June, respectively.

Under *quinine*, given 4 days later, the reaction was very small. The auricular rate showed a fall of only 50 oscillations, from 444 to 394, while the ventricular rose only 15 beats from 81 to 96.

In Fig. 2 reactions to the four alkaloids, similar to those of Fig. 1, are illustrated in a second patient, the test doses in this case being 0.4 of a

gramme. The results for the whole series of seven patients are summarised in Table II.

Of the four alkaloids tested, quinidine has uniformly the most powerful effect in reducing the rate of the auricular oscillations. For the seven patients the fall from the initial level to the minimal point averaged 161 oscillations per minute. Cinchonidine follows with an average fall of 126. *Case 4* constitutes single and slight exception to this order; in this patient the auricular rate under cinchonidine showed a slightly larger fall than that obtained under quinidine, the difference, however, being small (8 oscillations).

Third in order is cinchonine with an average fall of 109 beats. There is also a single exception here in *Case 5*, the auricular rate falling 13 oscillations lower with cinchonine than with cinchonidine. Quinine gives uniformly the smallest reaction, the average fall being only 86 beats per minute.

If the readings are taken when the curves are rising, for example at about 4 hours after the test doses are given, 3 p.m., it is found that this same order holds good, namely, quinidine, cinchonidine, cinchonine and quinine, the first being the most powerful.

As regards their effect on the rate of ventricular beating the alkaloids fall into a different order. The most conspicuous and usually the earliest rise of ventricular rate is brought about by cinchonine. In five of the patients the maximal point was reached within an hour after the administration of the test dose. In the two other patients the maximal ventricular rate was reached after the same interval as in the case of the other alkaloids.

Next in order come quinidine and cinchonidine, both causing about the same increase of ventricular rate. Quinine yields little or no ventricular reaction.

A further note remains to be added with reference to the effect of these alkaloids on the ventricular rate. It has been noted in these observations that before the rise occurs there is a tendency for the ventricular rate to fall slightly during the 20 or 40 minutes following the administration of the test dose. On looking back over our previous laboratory charts of the reactions to quinidine and hydroquinidine the same tendency is also to be seen. This preliminary fall did not occur in every case, but its appearance was sufficiently frequent to eliminate its being due to accidental variations.

*Protocols of case notes.*

- Case 1.* W. H. A man aged 53. Admitted to hospital on March the 6th, 1922. No history of rheumatic fever. Cardiac symptoms for 4 years. Mitral stenosis and auricular fibrillation, the last known to have been present for two weeks and probably present for 4 years. No signs of congestion. Heart slightly enlarged. Poor exercise tolerance.
- Case 2.* E. P. A man aged 29. Admitted on February the 25th, 1922. No history of rheumatic fever. Cardiac symptoms for 3 years. Mitral stenosis and auricular fibrillation, the last known to have been present for 14 months. No signs of congestion. No definite signs of enlargement. Poor exercise tolerance.
- Case 3.* W. O. A man aged 29. Admitted on March the 27th, 1922. No history of rheumatic fever, but of syphilis. Cardiac symptoms for 7 years. Mitral stenosis and auricular fibrillation, the last known to have been present for 4 weeks, and probably present for 7 years. No signs of congestion. Heart slightly enlarged. Poor exercise tolerance.
- Case 4.* J. M. A man aged 45. Admitted on March the 27th, 1922. No history of rheumatic fever. Cardiac symptoms for 4 years. Auricular fibrillation known to have been present for 22 months. No definite signs of congestion. Heart slightly enlarged. Poor exercise tolerance.
- Case 5.* G. C. A man aged 36. Admitted April 28th, 1922. No history of rheumatic fever. Cardiac symptoms for 4 years. Mitral stenosis and auricular fibrillation, the last known to have been present for 8 weeks and probably present for 10 weeks. No signs of congestion. Heart moderately enlarged. Good exercise tolerance.
- Case 6.* S. M. A man aged 39. Admitted on May the 31st, 1922. History of previous rheumatic fever. Cardiac symptoms for 5 years. Mitral stenosis and auricular fibrillation, the last known to have been present for 2 weeks, and probably present for 4 weeks. No signs of congestion. Heart moderately enlarged. Poor exercise tolerance.
- Case 7.* J. S. A man aged 59. Admitted on May the 11th, 1922. No history of rheumatic fever. Cardiac symptoms for 7 years. Fibrillation of auricles known to have been present for 10 months. No definite signs of congestion. Heart slightly enlarged. Poor exercise tolerance.

## CONCLUSIONS.

1. In clinical fibrillation of the auricles the rate of the auricular oscillations is reduced by the four alkaloids, quinidine, cinchonidine, cinchonine and quinine. The alkaloids are named in the order of their relative potency: this order is almost constant, and such exceptions as occur are trivial.

2. The relative effects on the ventricle are differently ordered: the ventricular rise is earliest and greatest under cinchonine, which appears

to possess a special action in this respect : quinine has little or no action on the ventricle in the doses given : quinidine and cinchonidine occupy an intermediate position.

3. The rise of ventricular rate which occurs in cases of auricular fibrillation treated with test doses of quinidine, hydroquinidine, cinchonidine and cinchonine is usually preceded by a brief preliminary fall of rate.

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# OBSERVATIONS ON A CASE OF VENTRICULAR TACHYCARDIA WITH RETROGRADE CONDUCTION.

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This paper deals with the clinical and electrocardiographic studies of a patient who was subject to paroxysmal attacks of rapid heart action, the frequency and severity of which virtually rendered the individual, otherwise normal, a cardiac invalid. The case is of interest because (1) it is a clear example of ventricular tachycardia, (2) the effects of several drugs were studied in connection with the irregularity, (3) the disorder was controlled by quinidine upon which the patient later became dependent.

Undoubted clinical examples of paroxysmal tachycardia originating at an ectopic site in the ventricle are rare. Past writings contain electrocardiographic records of about twenty cases considered by the authors as paroxysmal tachycardia of ventricular origin, but the evidence for the diagnosis is not entirely convincing in more than one-half of the cases. Frequently the records presented are those obtained during a paroxysm, so that the first or last beat is not recorded: consequently it is difficult and in some cases impossible to determine the exact origin of the paroxysms. Anomalous configuration of the ventricular complexes alone is not sufficient to establish their origin, since it is well known that aberrant ventricular conduction may appear during a high cardiac rate to return to normal when the tachycardia ceases.\*

In unmistakable examples of ventricular tachycardia the electrocardiogram shows the paroxysms to consist of a succession of ventricular extrasystoles, the first beat of the paroxysm having the same relation to the preceding normal mechanism as has the ventricular extrasystole, while the last beat is followed by a definite pause such as is frequently seen after a single extrasystole arising in the ventricle. Records of cases fulfilling these requirements have been published by Lewis,<sup>8</sup> Hart,<sup>5</sup> Cohn,<sup>1</sup> Hunt,<sup>6</sup> Vaughan,<sup>11</sup> Willis,<sup>12</sup> White,<sup>9</sup> and Gallavardin.<sup>4</sup>

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\* Records illustrating this point are shown in Figs. 242, 243, 247 and 248 of Lewis's book, "The Mechanism and Graphic Registration of the Heart Beat," London, 1920.

Failing to obtain a record of the first or last complex of a paroxysm, the next most reliable criterion is the appearance in the record of definite *P* deflections showing that the auricles are contracting at a slower rate and independent of the ventricles. Added security for the diagnosis is afforded by the occurrence of isolated ectopic ventricular complexes having the same configuration as those seen during the paroxysm. Robinson and Herrmann<sup>19</sup> have recently reported four cases which they interpret as ventricular tachycardia, but the diagnosis in three of their cases appears open to criticism on the ground that they may be examples of aberrant ventricular conduction occurring only during periods of rapid heart rate. The records from one of their cases, however (*Case 2*), show definite waves of auricular activity appearing at a slower rate and quite independently of the ventricles, which is, of course, strong evidence in favour of the diagnosis.

*Clinical history.* The patient, A. W., a female of 39 years, single, and occupied as a secretary, first came under observation in January, 1921. There was a vague history of rheumatic fever at 22 years of age, and a year later she had an illness lasting about two weeks, which was looked upon as typhoid fever. About ten years ago she first experienced slight attacks of "palpitation of the heart," but they were so ephemeral and occurred so infrequently that little attention was given to them. However, in the course of six or seven years they became more frequent and when continuing for a few hours were accompanied by faintness and vertigo. Finally in the early part of 1920 the attacks became so severe that the patient was forced to give up work and lead the life of a semi-invalid. It appeared from her account that latterly any slight exercise, such as walking rapidly or ascending stairs precipitated the attacks, which continued on different occasions from one to forty-eight hours. The patient had observed that the more severe attacks of rapid heart action never began nor ended abruptly, there being a transition stage, during which appeared what was interpreted as normal beats interspersed with abnormal ones. Subsequent records revealed the accuracy of this observation. The patient's account of the gradual development and ending of attacks suggested that she was not suffering from the ordinary paroxysmal tachycardia of auricular origin, in which the paroxysmal nature of attacks is a characteristic feature.

*Physical examination.* When first seen by the writer the patient had what she called a "mild attack," which had lasted for two days. On inspection of the precordial area with the patient sitting upright, one observed a definite irregularity. Five or more rapid and unusually forcible cardiac impulses alternated with two impulses which appeared normal as to rate, force, and position. The relatively thin chest of the patient made it possible to observe the curious change of position of the maximum cardiac impulse: situated over the conus during the paroxysm, it appeared at the apex with the less forcible beats. Each paroxysm ended abruptly and was followed

by a definite pause. This is clearly shown in the record (Fig. 1) obtained at the first examination.

An unusual variation in the volume of the pulse was observed, namely, during the tachycardia when the heart was beating forcibly against the chest wall, the pulse in the accessible arteries was barely palpable, whereas a quite normal volume was felt corresponding to the two normal beats. The systolic blood pressure was 85 mm. Hg during the paroxysms and 110 mm. with the normal contractions. Inspection of the neck vessels showed that with each period of tachycardia there was a conspicuous pulsation over both jugular bulbs and veins, more pronounced on the right, and similar to that seen in cases of insufficiency of the tricuspid orifice. This stopped short with each paroxysm, a pause followed and then two normal central venous pulses occurred. The exact relation of the jugular pulse to the cardiac mechanism is shown in Fig. 2, which is a simultaneous record of the electrocardiogram (L 2), and the right jugular pulse registered optically with the Frank capsule. The jugular tracing in this record shows a phenomenon which was very apparent on inspection, with the onset of a paroxysm the jugular pulse gradually increased in force for about six beats, reaching a certain maximum which was then maintained throughout the paroxysm. The conspicuous (A) wave in the jugular is no doubt due to the fact that during a paroxysm, auricular systole occurred while the ventricle was in a state of contraction; consequently the blood in the auricle was ejected backward into the veins. Further examination of the patient showed no demonstrable cardiac enlargement to percussion. On auscultation during the tachycardia one heard exaggerated heart sounds which were in sharp contrast to the quiet normal sounds accompanying the slow rate. At no time were any adventitious sounds audible.

After some insight into the nature of the cardiac disorder was obtained from the electrocardiogram, the patient was advised to come into the hospital for further study. For a few days she was kept at absolute rest and given triple bromides, gr. xv, q.i.d.. With this régime the cardiac mechanism was normal most of the time, though occasionally a single, or a series of two or three extrasystoles showing the same configuration as those seen during the attacks were observed. Fluoroscopic and X ray studies showed normal lungs and normal size and position of the heart and aorta. The Wassermann reaction on the blood was negative. Several competent observers failed to demonstrate any signs of heart disease. The systolic blood pressure was 115, diastolic 85. Continuing the bromide medication the patient was allowed to be up, but the attacks promptly reappeared, and, as the electrocardiograms showed, they were similar in every way to those observed at the first examination—a rapid succession of ventricular extrasystoles followed by a pause and two or more normal complexes.

Exercise was found to exert a definite influence on the severity of the attacks. For example, the more walking the patient did during the day the longer the abnormal mechanism continued after retiring. Occasionally

the mechanism consisted entirely of a continuous succession of ventricular extrasystoles which lasted at times for several hours after lying down (see Fig. 3).

After the foregoing observations were made the patient had occasion to leave the hospital. She returned, however, a few days later with an attack which had continued uninterruptedly for 48 hours, and she stated that it was the most severe one that she had experienced. The rate was 160 per minute. Signs of cardiac failure were present; both to the right and left the area of cardiac dullness extended 2.5 cm. beyond the normal boundaries previously found: the liver was definitely enlarged, and moisture was present at both lung bases. Although the heart was hammering against the chest wall the pulse was much diminished in volume and the systolic blood pressure was 85 mm. Hg. There was the same systolic pulsation of the jugular veins as described above. Even with the low blood pressure and other signs of circulatory impairment the patient was not particularly distressed, except for the symptoms of cerebral anemia. These improved considerably when she lay down. At this time and subsequently several attempts were made to influence the tachycardia by vagal pressure and also by ocular pressure, but neither procedure had any effect. A record taken during this attack is shown in Fig. 3.

Again with rest and bromides the cardiac mechanism became normal and continued so as long as the patient remained in bed, but with the slightest exercise, such as walking, the irregularity reappeared. Several electrocardiograms taken at different times showed by the configuration of the ventricular complexes that the same ectopic focus in the right ventricle was responsible both for the single and multiple extrasystoles, as well as for a continuous paroxysm. The therapeutic relief of the patient was further considered. Little help was obtained from a review of past cases of ventricular tachycardia, because diagnosis rather than therapy has been the chief point of discussion. In several of the recorded cases the patients had definite signs of heart disease, and the tachycardia appeared more or less as a terminal event; in others the attacks were short and disappeared without medication. The case herein recorded is, therefore, unique in several respects. In the first place the patient had no signs of heart disease, and so long as the sinus rhythm prevailed she was perfectly comfortable. Furthermore, attacks were induced by such slight exertion and the resultant derangement of the circulation placed such a restriction on the patient's activity that she was rendered virtually an invalid. In the search for a therapeutic agent which might exert some influence on the disorder, an opportunity was afforded to note the effects of several drugs.

#### *Effect of drugs on the tachycardia.*

The following observations were in each case controlled by electrocardiographic records taken at frequent intervals before and after the administration



of drugs. A hypodermic injection of sterile water was given as a control in the experiments with atropine and adrenalin.

*Atropine.* Prior to the use of atropine the patient was kept in bed to ensure that the mechanism remain normal. Atropine sulphate, 0.03 of a grain, was administered, and 15 minutes later a continuous tachycardia identical with that seen in Fig. 3 appeared and continued for six hours. No normal complexes were seen in any of the records taken at intervals during the attack. Subsequently another observation was made in which 0.02 of a grain of atropine was injected. This caused what might be called a mild attack, short paroxysms of extrasystoles interrupted by one or two normal complexes (as in Fig. 1). The other usual pharmacological effects of atropine were noted with both dosages, *i.e.*, paralysis of accommodation, dry mouth, etc..

*Digitalis.* When the heart was brought under the influence of digitalis (15 minims of the tincture being given daily for 7 days) T became inverted, and the attacks were diminished both in frequency and severity, so that the patient was able to walk about without distress. Under these conditions, atropine was administered, 0.03 of a grain being given hypodermically. There was an increase in heart rate from 60 to 84 per minute, but no change occurred in the cardiac mechanism. These observations suggested that the sinus rhythm might be maintained by therapeutic doses of digitalis acting chiefly on the vagus mechanism. Accordingly digitalis was given and the heart remained normal for three weeks even with exercise, but at the end of this time the attacks again appeared, although the drug was continued, and the patient developed mild symptoms of intolerance.

*Adrenalin.* Following the hypodermic injection of adrenalin (Parke-Davis Co. 1:1000 Sol.) in doses of 10-15 m., single extrasystoles appeared, followed a little later by a mild attack in which two normal complexes alternated with a run of 8-10 aberrant ones. This disturbance continued for about an hour, when the normal rhythm returned, the curves being very similar to those seen in Fig. 1.

*Nitroglycerine.* Spirits of nitroglycerine (0.03 of a grain) on the tongue caused no change in the normal cardiac mechanism which prevailed at the time the drug was given. The rate increased 10 beats per minute. The systolic blood pressure fell from 115 to 95, and the patient complained of cerebral symptoms similar to those experienced during mild attacks.

*Quinidine.* Powdered quinidine sulphate in capsules was given in doses of 0.4 of a gram three times a day. After a few days it was noted that the cardiac mechanism remained normal in spite of exercise. The dosage was then reduced to 0.2 of a gram, three daily, and continued for three weeks, during which time a normal mechanism prevailed. Exercise,

which had hitherto always caused aberrant beats to appear, now had no effect except to quicken the rate. To test the matter further, the drug was discontinued altogether, and after a few days the disorder again appeared. Exercise, such as walking or ascending stairs, caused attacks of the same nature as before.

The return of the tachycardia afforded an opportunity to study further the action of quinidine. It was found that a single dose, 0.4 of a gram of the drug, invariably terminated the paroxysms in from 30 minutes to 1 hour after given by mouth. A sufficient number of observations was made on this point to show beyond any doubt that quinidine in this particular case exercised a specific effect on the tachycardia. The patient was discharged from the hospital to report for examination once a month. Quinidine, 0.6 of a gram per day, was prescribed, and this was gradually reduced to 0.2 of a gram per day, a dose which appeared to be the minimal which would maintain the normal mechanism. During six months on this treatment the patient was comfortable and able to follow her usual occupation.

The continuance of the sinus rhythm for this period suggested that the tendency to ventricular tachycardia might be permanently abolished. To study this point the patient was again admitted to the hospital and quinidine discontinued, but after a few days without the drug the abnormality re-appeared, the records showing single aberrant complexes and paroxysms similar in every way to those seen previously. Re-administration of quinidine once more restored the normal rhythm.

The effects of atropine in promptly precipitating the tachycardia suggested an observation to determine if the drug exercised a similar effect while the heart was under quinidine. Fifteen minutes after 0.02 of a grain of atropine the irregularity appeared, typical curves of which are shown in Fig. 6. These curves also show some interesting effects of quinidine, which will be discussed later.

With the exception of three weeks spent in the hospital recently, the patient has taken quinidine for more than a year without any untoward effects. The dosage finally adopted was 0.2 of a gram once a day which, represents the minimum necessary to prevent the ventricular tachycardia, and, so far as our observations go, it appears that the patient's health is dependent on the drug. Mayer's reagent added to the urine shows a precipitate for 5-6 hours only, although the effect of the alkaloid apparently continues longer. It seems probable that the drug, when taken in the morning, exercises its action throughout the day, and as during sleep there is little tendency for the disorder to appear, the normal mechanism is maintained throughout the 24 hours.

#### *Discussion.*

The electrocardiograms obtained over a period of more than a year in the study of this case, fall into one of two categories: either the normal sinus rhythm prevails, or the normal rhythm is interrupted and occasionally

completely supplanted by ventricular extrasystoles arising from a common site in the right ventricle. The persistence of the ventricular rhythm with reversed conduction of every impulse to the auricle as seen in some of the severe attacks (Fig. 3), lasting up to 48 hours, suggests that we are dealing with what might be called a subsidiary pacemaker in the ventricle. According to our observations, exercise and drugs, *i.e.*, atropine and adrenalin, activate the ventricular impulse centre so that it dominates completely the heart beat, at times for a few seconds, again for several hours. Even when the heart is beating normally and there is little tendency for attacks to appear, as happens with quinidine, this ectopic focus may assert itself as a result of the administration of atropine. It should be mentioned, however, that the view taken as to the origin of the ventricular rhythm from an ectopic focus, is only a working hypothesis. On the other hand, there is some evidence to suggest that a rapid succession of extrasystoles emanating from the ventricle at a regular rate may be of the nature of re-entrant beats. Experimental observations pertaining to this point were published by Levy<sup>7</sup> and de Boer.<sup>8</sup> The foregoing case apparently fulfils some of the requirements for such a mechanism and may be an example of circus movement in the ventricle, but the time is scarcely ripe for finally answering this question.

In attempting to analyse the foregoing observations on the effect of drugs, particularly on the ventricle, one meets certain difficulties in the way of explanation. Unfortunately, the action of these agents on some fundamental properties of ventricular muscle is not as well known as it is in the case of the auricle. Here, as Lewis and others have shown, drugs, *i.e.*, digitalis, atropine, quinidine, produce their effect in part at least by influencing the refractory period and the transmission rate of auricular muscle. Although it is probable that future experimentation will show that these agents affect the ventricle in a somewhat similar fashion, yet until more information is available it seems well to state the facts and consider the results as they pertain primarily to (1) the vagus mechanism, (2) accelerator mechanism, and (3) the direct action of the drug on the heart muscle.

*The vagus mechanism.* The influence of the vagus on the ventricle is a debated issue. However, in the case herein presented the vagus mechanism exercised a definite control on the ventricular rhythm. Depression of vagal tone by atropine always released the ventricular rhythm except when the heart was under the influence of digitalis. The latter appeared to counteract the effect of atropine, a result which may be explained by augmented vagal tone resulting from digitalis. On the other hand, the constant administration of digitalis did not prevent the appearance of the ventricular rhythm caused by exercise. An interesting question in this connection is whether or not the stimulating effect on the accelerator mechanism overbalanced the increased vagal tone induced by digitalis? The precise effect which a direct action of digitalis would have on the results is uncertain, more especially

since the drug usually tends to promote rather than to abolish contractions arising prematurely in the ventricle.

*The accelerator mechanism.* In this category we may consider the effect of exercise and emotion, factors which provoked the ventricular rhythm. Similarly, the influence of adrenalin in inducing attacks suggests one of the known actions of this drug, namely, that of a stimulant to the cardio-accelerators.

*Drugs acting on the ventricle directly.* Under this heading may be placed one of the effects of digitalis, though its precise action is, as stated above, difficult to determine. More positive, however, are the effects of quinidine, under small doses of which the sinus rhythm remained undisturbed in spite of exercise and ordinary emotion. On the other hand, even large doses of quinidine failed to combat the effect of atropine in releasing the ventricular rhythm. It should be noted, however, that under these circumstances the attacks were not so severe as when atropine alone was given. Compare Figs. 3 and 4. It is apparent, therefore, that the immediate effects of atropine and quinidine were, in this case at least, diametrically opposite; quinidine in some way antagonised the attacks while atropine provoked them. If quinidine exercised a paralytic effect on the vagus, such action was relatively insignificant, and was completely overshadowed by the direct action of the drug on the heart. Furthermore, our results show clearly that quinidine controlled the ventricular rhythm by some action which left undisturbed the peripheral structure which atropine paralyzes. This result is in accord with the views of Dale,<sup>3</sup> who believes that the action of quinidine is not on the nerve endings, as is the case with atropine.

By comparing the curves in Fig. 4 with other records showing the first beat of a paroxysm, one notes that under quinidine there is a slight but definite lengthening of the interval between the normal and the succeeding extrasystolic complex. In other words, the extrasystole does not occur as prematurely with quinidine as without it. The  $R$ - $R'$  intervals, *i.e.*, the interval from the  $R$  peak of a normal complex to the  $R'$  peak of the extrasystolic following, is fairly constant, varying in different curves between 0.36 and 0.39 of a second. Under quinidine the interval is prolonged to 0.45 of a second, as a result of which the rhythmic auricular complex appears as a distinct deflection, notching the ascending limb of  $R'$  (see particularly the upper curve of Fig. 4). These observations decidedly suggest that quinidine lengthens the refractory period of the ventricle, rendering earlier prematurity impossible; and this view itself suggests that the power of quinidine to abolish the ventricular tachycardia is dependent upon a similar influence.

The constancy with which reversed conduction may occur is well illustrated in this case. Most records of paroxysms show it. Indeed the bundle appears to conduct the cardiac impulse with equal facility forward or

backward, according as the beat originates in the auricle or the ventricle. It is interesting to note that retrograde conduction usually begins with the first beat of a paroxysm (Figs. 1 and 2); although occasionally it starts later, as in Fig. 4. Whether the first premature beat of a paroxysm spreads to the auricle or not depends on whether the rhythmic auricular contraction is due and falls in the way of a retrograde response. This is well illustrated in Fig. 4. By spacing the rhythmic *P* deflections throughout these two curves one can predict that no retrograde responses will occur in the tachycardial cycles of the lower curve, because the auricle is contracted in response to the sinus when the retrograde impulse arrives. Similarly, in the upper curve of Fig. 4, only the last extrasystolic cycle is notched by a retrograde *P* deflection, because the retrograde impulse happens to reach the auricle before it is activated from the sinus.

#### SUMMARY.

1. A case of paroxysmal tachycardia of ventricular origin is recorded in which retrograde conduction occurred during attacks. Exercise and excitement appeared to be important factors in inducing the paroxysms.

2. Electrocardiograms showed that the paroxysms consisted of a succession of extrasystoles emanating from a common site in the right ventricle.

3. Observations on the effects of drugs, *i.e.*, atropine, digitalis, adrenalin, nitroglycerine and quinidine were made with the following results:—

- (a) Atropine in doses of 0.03 of a grain given hypodermically, always induced attacks except when the heart was under the influence of digitalis.
- (b) Digitalis minimised the severity of attacks but did not prevent them.
- (c) Adrenalin in doses of 10-15 m. hypodermically, induced mild attacks, that is, paroxysms consisting of 8-12 extrasystoles separated usually by two normal complexes.
- (d) Nitroglycerine (0.03 of a grain) caused the usual fall in blood pressure, but did not alter the normal mechanism prevailing at the time of its administration.
- (e) Quinidine exercised a specific effect in controlling the tachycardia, and has been given in doses of 0.2 of a gram daily for more

than a year without untoward effects. Several attempts to discontinue the drug resulted in a return of the cardiac disorder.

4. Quinidine did not affect the peripheral mechanism in the heart which is paralysed by atropine.

5. It is suggested that the ventricular rhythm observed during attacks may be of the nature of re-entrant beats.

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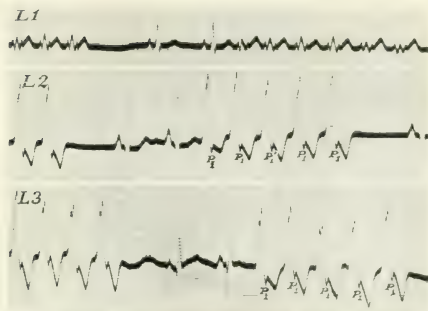


FIG. 1. Three leads showing the mechanism present at the first examination. Retrograde ventricular complexes are marked  $P_1$ . Time is fifths of a second.

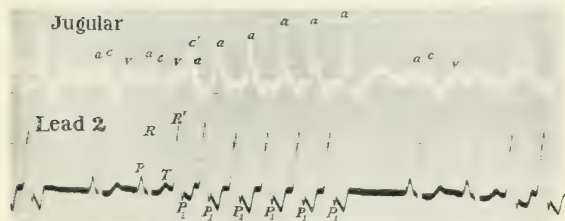


FIG. 2. A simultaneous record of the electrocardiogram (L2) and the aortic pulse registered optically.





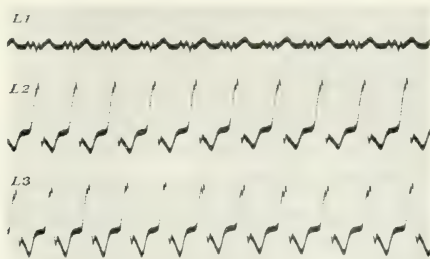


Fig. 3. Three leads taken during a severe attack lasting 20 minutes. Note that the mechanism consists of a continuous succession of ventricular extrasystoles, each one of which spreads to the auricle.

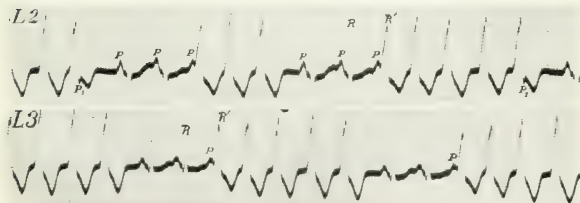


Fig. 4. Two curves showing the effect of atropine with the heart under the influence of quinidine. Note that the extrasystoles occur relatively later in diastole, so that the rhythmic *P* deflection falls on the ascending limb of *R*. Retrograde conduction either does not appear as shown in the lower curve, or it is confined to the last beat as illustrated in the upper curve. Time in fifths of a second.



# AN INVESTIGATION OF THE RELATION OF THE POSITION OF THE HEART TO THE ELECTROCARDIOGRAM

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New York.)*

IN the history of electrocardiography it has long been appreciated that a relation exists between the points of derivation on the surface of the body of the cardiac action current and the position of the heart in the chest. Waller chose certain points, called leads, because they were, as he said, favourable or unfavourable, meaning thereby that those leads were favourable which yielded large deflections. But since the introduction of the galvanometric method into human physiology, the use of three leads, proposed by Einthoven, has been generally adopted. There has been no serious criticism of the usefulness of the arrangement proposed. The utilisation of this method has, on the contrary, given occasion for extending knowledge based directly on this convention.

The electrocardiogram, which is derived from the usual three leads, although in large measure constant in form in the same individual over long periods of time, is, nevertheless, known to undergo certain changes in outline when, the leads remaining constant, the heart is caused to alter its position in the chest. Einthoven<sup>3</sup> pointed out that this result took place when the body was rotated from side to side, for under these conditions the heart rotated on a vertical axis (head to foot) and permitted the projection on lead *I* of an electrical potential which lay in the sagittal plane. In like manner he showed that in breathing, the form of the electrocardiogram, certainly the direction of potential in the region of the *R* wave, altered as a result of rotation of the heart on an antero-posterior axis. An exaggeration of this effect is seen when the position of the body as a whole is made to change from the recumbent to the erect position. In dextrocardia, when the position of the heart in the chest is reversed, the electrocardiogram is also reversed.

The phenomena just reviewed are well known. It is, however, less well known how great is the influence which the exact position of the heart in the chest exerts on the electrocardiogram. This position may be described roughly in terms of an angle which the heart makes with the horizon. This angle is formed by a transverse horizontal line and a line drawn from the junction of the curve of the right auricle in the röntgenogram, with that of the ascending aorta to the apex of the heart.

That this angle, which gives a measure of the inclination of the heart in the chest, has a distinct influence on the form of the electrocardiogram and on the direction of potential, that is to say, on the electrical axis, is shown by Einthoven's observations on the effect of respiration.

The significance of these changes of the anatomical angle on the form of the curves, and on the direction of potential, it would be simple enough to appreciate, were it not that the subject is in general complicated by the existence of curves of so-called right and left ventricular preponderance. Curves such as these are said to represent, sometimes enlargement, sometimes hypertrophy of the wall either of the right or left ventricle. How to interpret curves believed to indicate the presence of disproportionate unilateral enlargement has often been the subject of speculation.\* This was especially the case when on dissecting and weighing hearts post-mortem, which yielded one or other type of curve during life, there failed to appear that disproportion in the weights of the ventricles which it was anticipated would be found.<sup>5</sup>

We have no data to offer which resolve the confusion caused by this failure of the hearts when dissected to yield weights which the curves prepared one to find. We have, on the contrary, confined ourselves to a systematic investigation of the influence which differences in position of the heart in the chest actually cause in electrocardiographic curves. It is naturally impossible in the human subject to go further in the effort to alter the relation of the heart to the thorax than has already been attempted during respiration and on changing the position of the body as a whole, as has been done by Einthoven. To go further in animals involves manipulations which defeat the ends in view. But in the human subject we have devised a method of altering the relation of the anatomical angle of the heart to the chest, or more accurately to electrocardiographic leads, in whatever way it suited us, and by this means of learning precisely, in the same subject, what changes are wrought in the curves by changes in cardiac position.

We have assumed the correctness of Einthoven's theory of the equilateral triangle. In two individuals we have constructed the largest equilateral triangles we could lay on the chest, of a size such that the apices of the triangle representing the right and left arms, lay in the frontal, usually the mid-frontal, plane of the body: the apex of the triangle representing

\* This subject was recently reviewed fully in a paper, the reference for which is given in the bibliography.

the left leg lay below the level of the ensiform cartilage, but in a frontal plane anterior to that occupied by the other two (Fig. 18). We found in point of fact that the size of the triangle (the sides measured 35 cm.) was sufficiently large so that electrocardiograms (Fig. 3) of the three leads taken simultaneously by three galvanometers resembled, in all but details, controls of the three usual limb leads (Fig. 2), also taken simultaneously by three galvanometers. We found also that the curves corresponding to leads *I* and *III* equalled lead *II*, in accordance with Einthoven's formula (Table I).

TABLE I.

*Showing the correspondence of the triangles and the electrocardiograms, as well as the anatomical angles and electrical axes.*

Column A-B	Column C-D	Figs.	Observed Values of <i>R</i> Connected in accordance with Standardization and <i>I</i> and <i>II</i> .		Derived Value of <i>R</i> lead <i>II</i> .	Observed Value of <i>R</i> lead <i>II</i> .	Anatomical Angle.	Electrical Axis.*
		2	2.59	8.80	11.39	11.58	46°	89°
1	1	3	1.31 +	11.40 =	12.71	11.63	46°	-84°
2	9	4	12.14	5.58	6.56	7.18	6°	3°
3	8	5	9.84 +	10.98 =	1.14	1.61	34°	-38°
4	7	6	2.58 +	6.49 =	3.91	3.18	74°	-67°
5	6	7	4.74	6.34	-11.08	-12.66	-114°	-112°
6	5	8	19.25	1.68	-17.57	-17.34	154°	-154°
7	4	9	11.25	1.36	-9.89	-8.72	166°	-156°
8	3	10	7.11	10.61	3.50	4.78	126°	123°
9	2	11	1.06	15.52	16.58	17.54	86°	87°

\* Einthoven (W.), Bergansius (F. L.), and Bijtel (J.). "Die gleichzeitige Registrierung elektrischer Erregungszustände mittels zwei oder mehr Galvanometer und ihre Anwendung auf die Elektrokardiographie." Arch. f. d. ges. Physiol., 1916, CLXIV, 167.

In taking these electrocardiograms simultaneously and in order to obtain satisfactory results, it was necessary to overcome certain technical difficulties. Einthoven in his experiments and Lewis in his both employed Cambridge instruments having two string carriers. For the purpose for which it was used this arrangement is adequate. When the curves are to be used for calculating the direction of potential, it is, however, preferable not to employ this apparatus, for it is not easy with it to place the two strings in such positions in the magnetic field at which proportional deflections to both sides of zero can be expected. We desired also to escape the difficulties found by Einthoven which attend setting up galvanometers in tandem, although the problem of illumination and of time-marking are simplified by his arrangement.

To avoid certain of these difficulties we adopted the following plan. Two galvanometers (Williams-Hindle model) were set parallel and a third (Edelmann model, modified to attain greater rigidity) was placed at right angles to these (Fig. 1). The illumination was provided by three Siemens-Schuckert arc lamps, and the optical systems were those of Einthoven. To photograph the string deflections of the three galvanometers on a single camera the beam of light from galvanometer 3 was deflected by two  $90^\circ$  prisms, and that of galvanometer 1 by one prism. This plan was for our

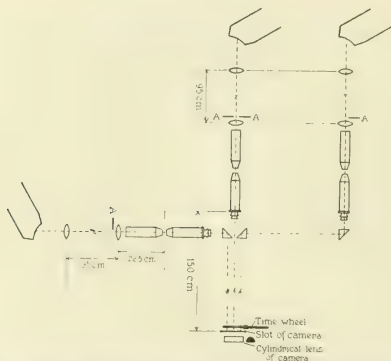


Fig. 1. Diagram showing the arrangement of the galvanometers. The details are given in the text.

purposes the most economical in space. An effort was made at first to provide for the time ordinates by interrupting the three several beams of light at the usual points between the arc light and the condensing microscope by three motors driven synchronously with a tuning fork. The difficulty of manipulation was, however, great, and was abandoned in favour of a simpler scheme. A motor of the usual (Cambridge or Hindle) type driven synchronously with a tuning fork in the usual fashion was placed just in front of the camera slit. Instead of the wheel having the short spokes commonly employed we constructed one having spokes 9.0 cm. long, the margins of the spokes being radii of the circle. The width of the spokes was such that at the rate of rotation employed ( $360^\circ$  in 0.2 second), the image cast by four spokes was 0.3 mm.; the fifth spoke cast a shadow twice this width. The edges of the shadows are, of course, parallel. The axis is at

the level of the cylindrical lens. If the beams of light of the three optical axes are parallel between the prisms and the camera and at the same level they fall on the cylindrical lens of the camera so that single straight ordinates are cast: failure to attend to these details results in broken lines. As our records show, quite satisfactory ordinates are made by this system. The optical difficulties which are occasioned by setting the galvanometers in tandem and by attempting to synchronise more than one motor with a single tuning fork are avoided. The three fields are separated sharply by screening the three galvanometer systems in the way shown at the points marked A (Fig. 1).

The leads were taken with lead electrodes.<sup>2</sup> Compensation and standardisation were accomplished in accordance with the technique described by Einthoven, Bergansius and Bijtel.<sup>4</sup> The resistances were taken for each lead in each position, and were always sufficiently low (usually 600 to 1,000 ohms; rarely 2,000 ohms) to prevent distortion of the curves. The standards arranged in accordance with readings of one and the same milliammeter were photographed in each instance, the string being deflected by steps of 1.0 millivolt, the patient being in circuit. In all calculations, the amplitude of the deflections was corrected in accordance with the standard deflection.

Having found this preliminary portion of our investigation sufficiently satisfactory, we proceeded to take curves from points on the chest (Fig. 18) indicated by the apices of our triangle when we rotated this about an anteroposterior axis (the point marked over the sternum in Fig. 18) through arcs of 40°. First we rotated the triangle in a clockwise direction so that the position of the right arm lead assumed succeeding positions from 1 to 9 (Figs. 3 to 11, and Fig. 12, A1 to A9). Under these circumstances the arrow, which indicates the position of the anatomical axis of the heart, naturally

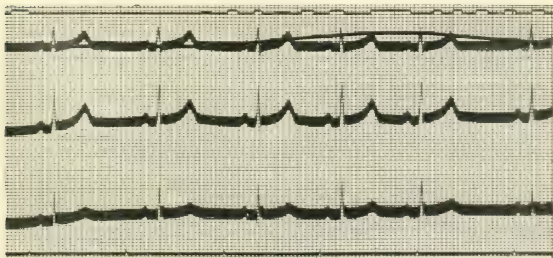


Fig. 2.

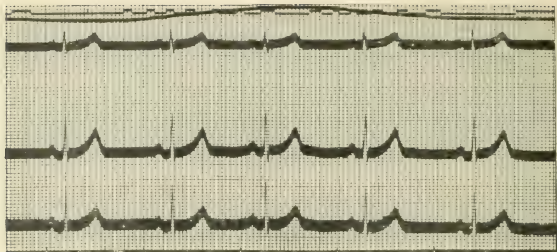


Fig. 3.

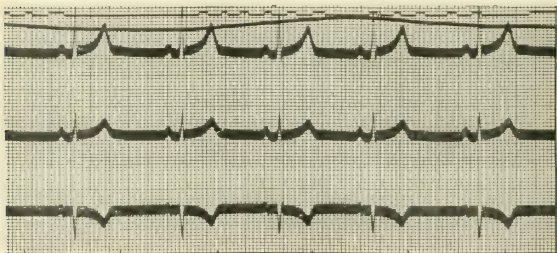


Fig. 4.

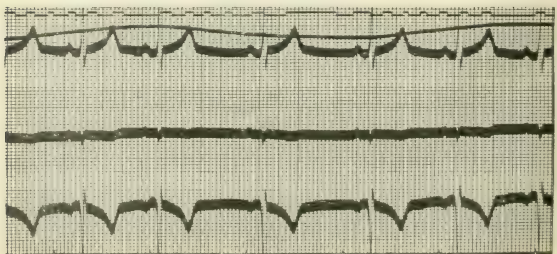


Fig. 5.



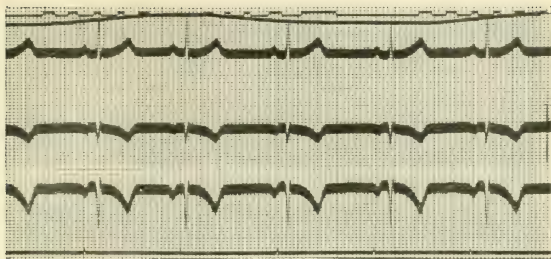


Fig. 6.

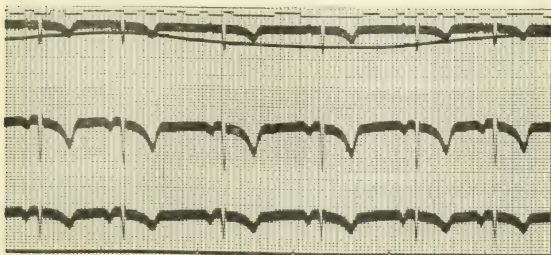


Fig. 7.

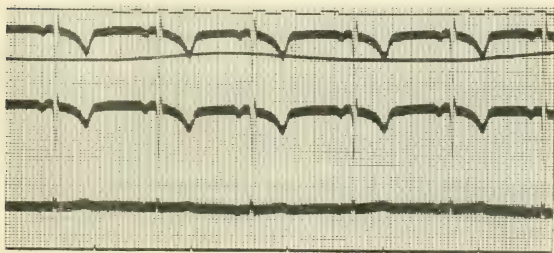


Fig. 8.

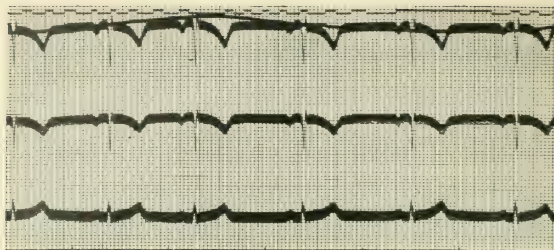


Fig. 9.

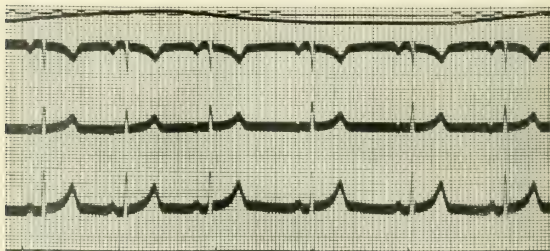


Fig. 10.

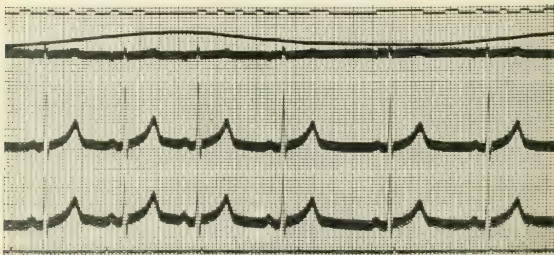


Fig. 11.

Figs. 2-11. In each curve three leads were taken simultaneously by three galvanometers. The leads in Fig. 2 are the usual 3-lead leads. The derivation of each of the other leads is shown in Fig. 12. The ordinates equal  $10^{-4}$  volts; the abscissae 0.04 of a second. The curve above is a respiratory curve; each mark of the signal indicates a change of 100 c.c. of tidal air. The original curves are sharply contrasted black and white; no half tones are lost by this method of reproduction.

remained fixed, and formed a variety of angles with the sides of the triangle as it rotated. What the values of these angles formed by the arrows and the horizon would actually be is given in the diagram in column B, for here the triangle, together with the arrow shown in column A, is rotated back so that the usual position of the RA-LA line parallel with the horizon is maintained. The arrows, it will be seen, have rotated in a counter-clockwise direction. The electrocardiograms corresponding to each of these positions are reproduced (Figs. 3 to 11).

Next we rotated the triangle in a counter-clockwise direction (diagrams in Column C, Fig. 12) so that the point RA of the triangle moved necessarily from position C1 to position C9 and onward around the circle to position C2. Having, as before, established the relations of the arrow, which remained fixed, to the sides of the triangle as it rotated, the triangles and arrows were turned back to the conventional RA-LA positions shown in column D. The angles formed by the arrows with the horizon under the circumstances are shown. It is obvious that diagram C2 is identical with diagram A9 and Fig. 11; C3 with A8 and Fig. 10; and so on (Table I).

It is necessary to point out a possible source of confusion in these diagrams. The angle  $46^\circ$  in diagram A1 (and also in B1, C1 and D1) is the actual anatomical axis of the heart in this individual in the recumbent posture measured in a röntgenogram during the inspiratory phase of respiration (Fig. 19). The arbitrary method of rotation of the leads which we adopted resulted in creating anatomical axes which obviously are unlikely to exist in nature. In point of fact, it is not probable that any anatomical angles other than those lying between  $+6^\circ$  (B2) and  $-86^\circ$  (D2)\* are likely to occur. These are, however, possible. If in a normal heart such as this the heart rotates so that the anatomical axis of  $46^\circ$  (B1) were to swing to the position of  $6^\circ$  (B2), a change in the form of the electrocardiogram takes place, and this form resembles that associated with left ventricular preponderance (Fig. 4). A difference will be pointed out later. If, on the other hand, it is caused to rotate in the opposite direction, so that instead of  $46^\circ$  (D1) it assumes the position of  $86^\circ$  (D2) a characteristic change in the electrocardiogram does not take place, but if the rotation is carried  $40^\circ$  further, to  $126^\circ$  the curves which appear resemble those associated with right ventricular preponderance (Fig 10).† Here again a difference occurs which is to be pointed out later. The rotation of the triangle of leads has been continued both in the clockwise and in the counter clockwise directions, but the angles made by the arrows with the horizon cannot now be regarded as actual anatomical axes, for these are obviously improbable, but as theoretical anatomical angles (Table I). Assuming, however, that such

\* The signs of the angles, both anatomical and electrical, are given as is usual in electrocardiography; + is below, — above the transverse line.

† It would have been desirable to take curves at an anatomical axis somewhat less than  $126^\circ$ . At  $100^\circ$ , curves usually designated as associated with right ventricular preponderance might have appeared. But even this is an unlikely anatomical axis.

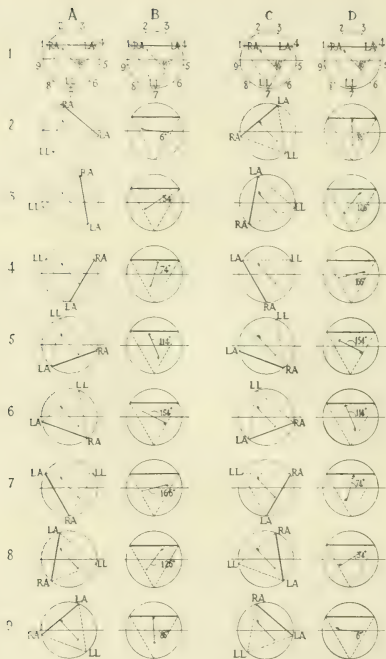


FIG. 12. The columns A B and C show each a row of circles containing equilateral triangles. In columns A and C are given the arrangement of leads as the triangle is rotated about its centre. In columns B and D the triangles with their contained arrows, shown in columns A and C, are rotated back to the familiar RA-LA positions. The angles given are, in the top row, the actual anatomical angles seen in the röntgenogram in the recumbent position during inspiration, and the theoretical angles obtained under conditions described in the text. In column A the triangles are rotated clockwise; in column C, counter-clockwise. The arrows rotate counter-clockwise in column B and clockwise in column D. Which electrocardiogram was derived from each of these positions is given in Table 1.

anatomical axes exist, the electrocardiograms which were obtained in successive positions were curves which yielded electrical axes corresponding to those within ranges with which one is familiar, that is to say, they were curves which range between  $-67^\circ$  and  $+123^\circ$ ; three other curves (Figs. 7, 8 and 9, Diagrams B5, B6 and B7, and D6, D5 and D4) are less frequently seen.

The striking point in studying these curves obtained from unusual anatomical points is their resemblance to curves regarded as indicative of ventricular preponderance, especially so far as concerns the *Q, R, S*, complex. There is, however, a difference between them already referred to. This difference consists in the fact that in all instances the signs of the *R* waves and the *T* waves are the same. This phenomenon is to be anticipated under the conditions. In curves of ventricular preponderance, at least in curves from cases in which the heart is known to be abnormal, the signs of the *R* waves and *T* waves are usually unlike and opposite. A difference in the *P* waves also exists. These differences we wish merely to point out. We hope later to present curves which bear on these points.

We wish now, however, to point out that the form of the curve seen in Fig. 4 is strikingly similar to certain curves made of normal individuals. In a series of electrocardiograms made in May, 1919, a number of these appear. They were obtained from two hundred and eight soldiers, selected by their officers before discharge as being normal individuals.<sup>1</sup> Among these men, deemed to be normal, six showed the signs of left ventricular preponderance and three of right ventricular preponderance (Table II). The test of exercise was applied to these men. This consisted of hopping one hundred times on the left foot, and was considered to have been satisfactorily performed when the pulse rate returned in two minutes to within ten or less beats, and the blood pressure to within a few millimetres of the figures found in the control period, and when there was no dyspnoea. In two of the nine cases the test was described as not completely satisfactory (*Case 3*), and as having occasioned moderate dyspnoea afterwards (*Case 7*). In the former case the heart may have been enlarged: there was no murmur at the apex, but a systolic one at the base. The blood pressure did not fall to normal two minutes after exercise. The man had scarlet fever at thirteen and tonsillitis at ten. These factors might have accounted for the facts found were it not that he had the day before been discharged from hospital on account of a minor illness. His condition was apparently not good, even if he were considered free from heart disease. In the other case (*Case 7*), in addition to moderate dyspnoea, neither the systolic nor the diastolic pressures returned to the level of the control period. The pulse rate behaved, however, in a normal fashion. This man had had only measles. On physical examination his heart was normal. Of the other cases, although histories of infectious diseases were given, there was nothing in the physical examination to lead one to doubt the soundness of their hearts.

The curves of six of the nine men showed, as has been said, curves resembling left ventricular preponderance, that is to say, deep *S* waves in

TABLE II.  
Data of nine soldiers showing curves attributed to right and left ventricular preponderance.

Case No.	Age	Actions.	Past History.	Record during Service.	Heart.	Nature of Response.	Exercise Test.				Ventricular Preponderance.			
							Heart Rate.	Blood* Pressure.	Left Ekg.	Right Ekg.				
1	4	24	Chateau Thierry, St. Mihiel, Belleau Woods.	Measles at 16, days on active service after two days. Wounded in knee.	Normal in size. No murmurs either in erect or recumbent position.	Normal. (This man only hopped 60 times, owing to injury to knee.)	Rose from 76 to 88, and fell to 74 two minutes later	112-74 124-82 114-78	28	42				
2	13	50	St. Mihiel, Argonne, Meuse.	He said he had been gassed but was not in hospital.	Normal in size. Systolic impurity on inspiration in erect position	Completely satisfactory.	Rose from 84 to 88, and fell to 71 two minutes later	102-80 110-61 106-80	32	42				
3	23	25	Argonne, Meuse.	Had been in hospital six days, came out one day before examination.	Transverse measurement 15.4 cm., area 120 sq. cm. Syst. murmur both in inspiration and expiration at base, not at apex.	Not completely satisfactory.	Rose from 86 to 102, and fell to 86 two minutes later	126-70 178-60 153-62	33	37				
4	54	26	Hindenburg Line, Argonne.	Gassed, but not in hospital.	No murmurs either in recumbent or erect position	Satisfactory.	Rose from 76 to 98, and fell to 84 two minutes later.	124-68 128-66 128-70	34	40				



5	30	30	Under fire. Never through whole. Typhoid fever at 17. Pneumonia in 1918.	Cardio-respiratory murmur in recumbent position only	Moderately good. No dyspnoea.	Rose from 88 to 128, and fell to 124.	148-90 188-90 122-82	36	32
6	64	30	Chateau Thierry. St. Mihiel. Champagne. Argonne.	Systolic expiratory murmur which disappeared in erect position, this did not reappear after exercise.	Satisfactory.	Rose from 80 to 100 and fell to 80 two minutes later	132-72 143-72 132-70	40	46
7	132	30	Gosnes	Cassed, but went back to service.	No murmurs, either recumbent or erect position.	Before exercise 68, rose to 88, and fell to 60.	132-70 188-88 173-94	41	68
8	197	23	Argonne. Verdun.	Scarlatina at 7. Measles at 10. Measles at 14. Pneumonia at 15. Muscular rheumatism (so called) in August, 1918.	No murmurs in either position.	Rose from 68 to 96 and fell to 78 two minutes later	98-64 118-70 110-64	43	83
9	214	23	Measles. Pertussis. scarlet fever, diphtheria, dysentery before 10. Inflammatory rheumatism at 18. Appendicitis in Dec., 1918.	No murmurs in either position.	Quite satisfactory.	Before exercise 76, rose to 112 and fell to 84.	130-70 140-50 140-58	56	71

\* First figures were taken before exercise; the second, immediately afterward; the third, two minutes later.

lead *III*. In three (*Cases 1, 4 and 6*), the *T* wave was also inverted (Fig. 13\*). In an additional case (*Case 3*), when a curve was taken in the erect position, the *T* wave became inverted (Fig. 14). Here the *Q.R.S.* complex also changed: the *R* wave was substituted by a *Q* wave and the *S* wave became an *R* wave. When the erect position was assumed there was no change in the curves of the other two men (Fig. 15).

To these cases, the cases of two normal civilians may be added—a man and a woman. In both, the curves were like those of the three soldiers: there were deep *S* waves and inverted *T* waves in lead *III*. The records

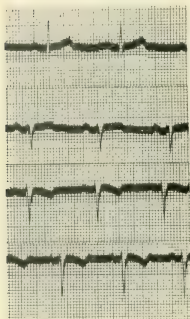


Fig. 13.

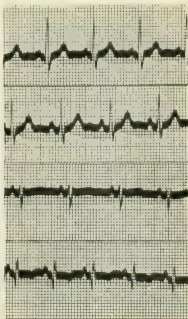


Fig. 14.

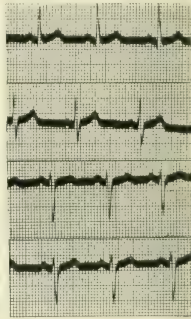


Fig. 15.

Fig. 13. Leads *I, II* and *III* from above downward. The fourth strip is lead *III* taken in the erect position. Ordinates and abscissæ as in Figs. 2-11. The curves show deep *S* waves in lead *III*. The *T* waves in both strips of lead *III* are inverted.

Fig. 14. Same as above. *T* in lead *III* is upright in the 3rd strip. It is inverted in the 4th strip taken in the erect position.

Fig. 15. Same as above. The *T* waves in both strips of lead *III* are upright.

of this hospital were not searched for other similar cases, but numerous ones could, without doubt, have been found.

It is to be noted that the anatomical angles of the soldiers' hearts were  $28^{\circ}$ ,  $32^{\circ}$ ,  $33^{\circ}$ ,  $34^{\circ}$ ,  $36^{\circ}$  and  $40^{\circ}$  respectively. The direction of potential in the region of the *R* waves in the corresponding cases may be given roughly as  $42^{\circ}$ ,  $42^{\circ}$ ,  $37^{\circ}$ ,  $40^{\circ}$ ,  $32^{\circ}$  and  $46^{\circ}$  respectively. In curves taken in this way exactness is not possible on account of phasic alterations. These were

\* This electrocardiogram is taken from *Case 4*, and is characteristic of the group.



clearly all more or less transversely lying hearts, presenting small anatomical angles. With one exception, they were smaller than those next to be described. The angles formed by the electrical axes were also small, relatively speaking. Both sets of figures are to be contrasted with those which follow.

These were cases (*Cases 7, 8 and 9*) in which the *S* waves in lead *I* were deep and resembled curves of right ventricular preponderance (Fig. 16). The *T* waves in lead *I* were directed upward as were likewise the *T* waves

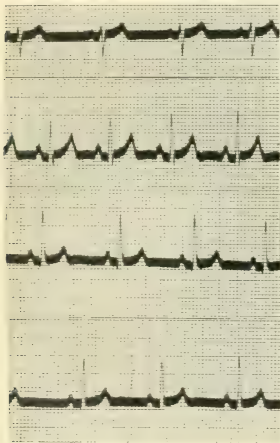


Fig. 16.

Fig. 16. Same as Fig. 13. The curves show deep *S* waves in lead *I*. The *T* waves in all strips are upright.

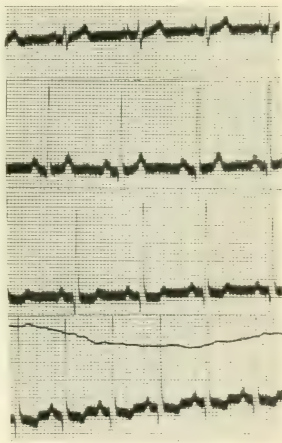


Fig. 17.

Fig. 17. Same as above. The *T* waves in the 4th strip, in the erect position are inverted.

in lead *III*. It is noteworthy, however, that in two cases (*Cases 7 and 8*) the interval between the *R* waves and the *T* waves was flat. Unfortunately, when the posture was changed from the semi-recumbent to the erect position, not only in these but also in the preceding six cases, only lead *III* was photographed. We have, therefore, no record of the behaviour of lead *I* under these circumstances. In *Case 8*, the *T* wave in lead *III* became inverted on changing to the erect position (Fig. 17).

A number of the facts reported in connection with these nine cases are recorded now for the purpose of description only. It is a matter of interest that in men, presumably healthy, curves resembling those of both right and left preponderance should appear. It is remarkable that the anatomical angles of the hearts yielding deep *S* waves in lead *III* should be small: that the curves yielding deep *S* waves in lead *I* should be large. Of striking importance is the fact that in the curves showing deep *S* waves in lead *III*, a number presented *T* waves which were inverted. These are the curves, more than the others, which resembled those of the individual described in the earlier part of this study in whom the location of the leads was shifted, or perhaps it were better to say, in whom the angle of the heart in respect to the leads was shifted from  $46^{\circ}$  to  $6^{\circ}$ .

It is facts such as these which have led us to draw attention afresh to the conception that the position of the heart in the chest has an influence on the form of the electrocardiogram, and that this influence may be far reaching. From the influence of position, the effect on the curves of enlargement of the heart must be distinguished. We wish at this time to go no further than to point out that this is a relation which must be taken into consideration when an opinion is formed on the character of enlargement from electrocardiograms.

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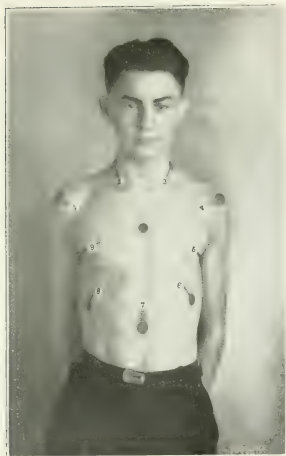


Fig. 18. This figure shows the sites at which the electrodes were applied. They are the points at which the angles of the equilateral triangle fell when the triangle was rotated. The successive triangles can be reproduced by joining points, such as 1, 4 and 7; 2, 5 and 8, etc.. In order to assume these positions, the triangle was rotated about its horizontal axis indicated by the circle situated over the sternum. Points 6, 7 and 8 are anterior to the mid-frontal plane, 6 and 8 assuming an intermediate position.



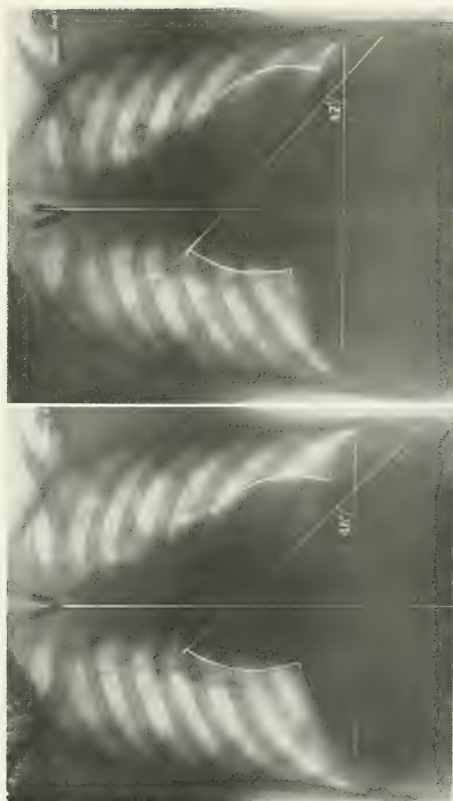


FIG. 19. Two telocenters, same location in the anteroposterior plane, the one at the left during inspiration; the one at the right during expiration. The angles made by the long diameters with the horizon are in the former 46°, in the latter 42°. The intersection of the two lines is the apex of the heart, as is readily seen in the original unprocessed photographs.



# ON THE RELATION OF THE POSITION OF THE ENLARGED HEART TO THE ELECTROCARDIOGRAM.

By ALFRED E. COHN.

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New York.*)

IN the preceding publication,<sup>1</sup> we described the influence which it is possible to exert on the electrocardiogram by changing the position of the normal heart in the chest of an individual. We did this by altering the position on the chest wall of the electrocardiographic leads. We showed that the influence produced was profound, so profound in fact that it was possible in certain positions of the electrodes to simulate, at least so far as the *Q.R.S.* complex was concerned, curves of ventricular preponderance, both right and left. We were able to show in a normal heart that at least in one position, when the artificial anatomical angle was  $6^\circ$ , a set of curves could be obtained which resembled in their main details the curves of certain soldiers as well as those of certain civilians. In these individuals the angles of the hearts were, relatively speaking, low. We suggested, therefore, that the low angle, that is to say, the position of the heart, might account for curves of preponderance, and that in curves of this nature the question of cardiac hypertrophy and consequently of heart disease need not, as it had been in the case of the male civilian, be raised. We emphasised the fact that the sign of the *T* waves in these cases was identical with that of the *R* waves in all instances, and stated that in the curves of preponderance associated with heart disease this identity of sign in the two waves was not usual. At the same time, we indicated our intention of supplementing the data taken from the curves then published, by reproducing others taken from patients having heart disease. We describe now, therefore, the appearance and behaviour of curves taken from one case in which the electrocardiographic signs of left ventricular preponderance (deep *S* wave in lead *III*) were found (Fig. 1); and of another case in which the signs were those of right preponderance (deep *S* wave in lead *I*).

L.V.P. is a male, 43 years old, who suffered from whooping cough : influenza in 1888, 1894 and in 1918. He drank 10 to 15 glasses of beer a day and drank whisky moderately. He smoked 40 cigarettes a day. In 1918 he was passed in the first class for life insurance : in 1919 the systolic blood pressure was 165 mm. Hg. In December, 1920, he began to complain of exhaustion, and occasionally of severe headache. These became more and then somewhat less frequent. In November, 1921, he excreted 37.5 per cent. of phthalein, 22.5 per cent. in the first, and 15 per cent. in the second hour. Now the area of cardiac dullness, measures, on percussion, 5.0 cm. to the right and 11.0 cm. to the left of the sternum in the 5th spaces. There are no murmurs. The anatomical angle is  $29^\circ$ . The pulse rate is 96, the blood pressure is 210 mm. Hg. systolic, and 150 diastolic. The Wassermann reaction is negative. The urine contains albumen, hyaline and granular casts and a few red and white cells. The diagnosis is chronic nephritis.

R.V.P. is a female 9 years old. In 1917 she was taken with fever and sore throat. Soon a diagnosis of heart disease was made. She failed to regain her strength. In 1918 she had measles. In 1920 she suffered from another attack of fever for 16 days, during which her joints may have been affected. In April, 1921, there was an attack of pneumonia lasting two weeks. In August, 1921, she developed œdema of the feet and abdomen. She now has a large heart, the area of cardiac dullness being 3.0 cm. to the right in the 4th space and 11 cm. to the left in the 6th space on percussion. The physical signs on auscultation, a crescendo presystolic murmur especially, indicate the presence of mitral stenosis. The angle of the heart is  $43^\circ$ . The urine occasionally shows a trace of albumen and an occasional hyaline cast as well as a few red and white blood cells.

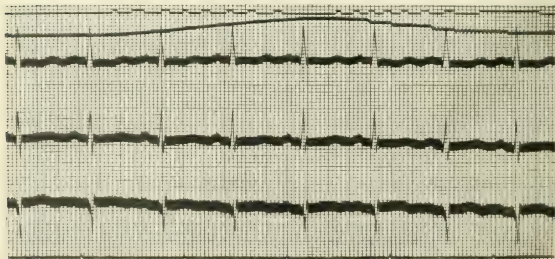


Fig. 1.



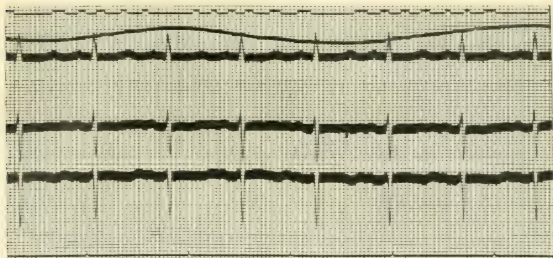


Fig. 2.

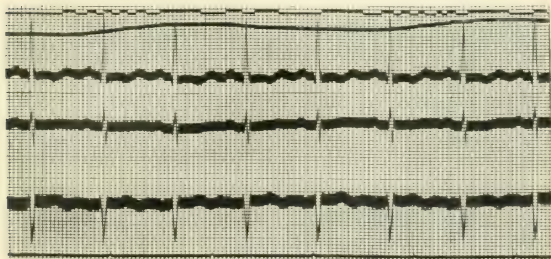


Fig. 3.

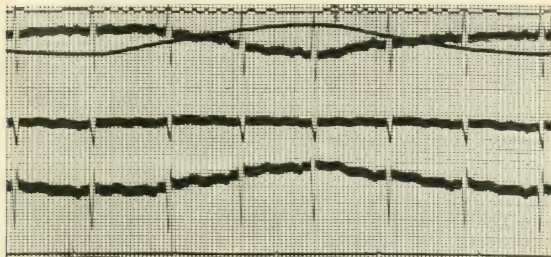


Fig. 4.

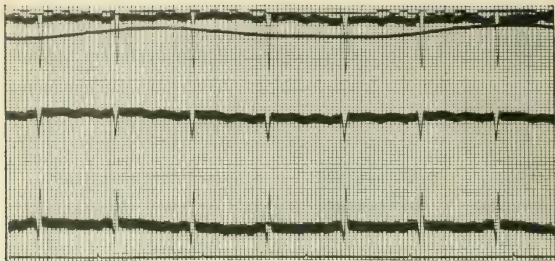


Fig. 5.

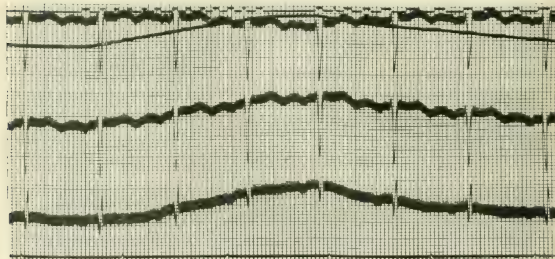


Fig. 6.

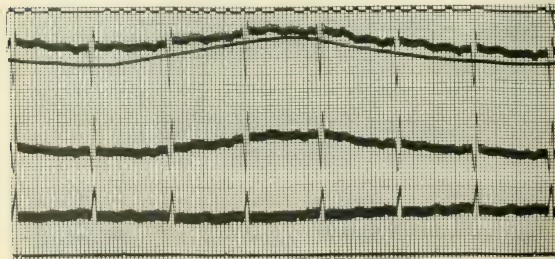


Fig. 7.

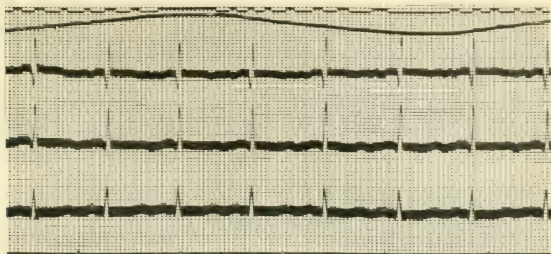


FIG. 8.

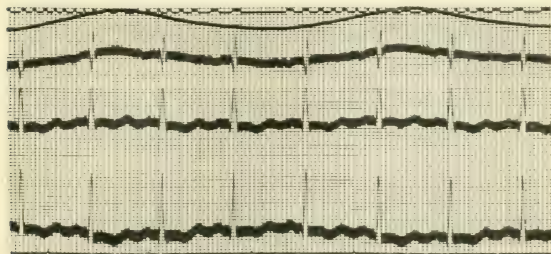


FIG. 9.

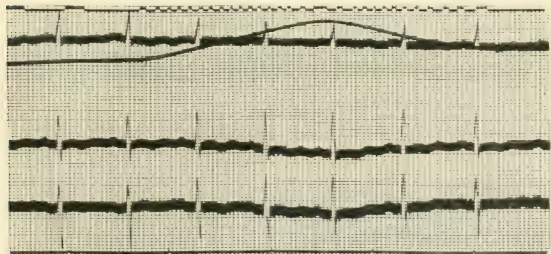


FIG. 10.

Figs. 1-10. In each figure curves are presented from three electrocardiographic leads, I, II and III, from above downward. They are taken synchronously by three galvanometers. The technique of taking them is given in an earlier paper.<sup>1</sup> Divisions of the ordinates equal  $10^{-4}$  volts. Divisions of the abscissa equal 0.04 of a second. Fig. 1 of the usual limb leads. In Fig 11 is given the derivation of each of the other leads. The uppermost curve is a respiratory curve; each mark of the signal indicates a change of 100 c.c. of tidal air.

The technique was identical with that employed by us in the case already reported.<sup>1</sup> In the case (hereinafter referred to as L.V.P.) in which the heart yielded curves of left ventricular preponderance, the anatomical angle was 29°. On rotating the triangle of leads it was found that the curves could be described as left preponderance curves, not only at this angle but at all angles between +69° and -51°, a range of 120° (Figs. 2, 3, 4 and 10). But curves which could be described as indicating preponderance of the right ventricle were obtained between -91° and -171° (Figs. 5, 6 and 7).

TABLE I.

*Showing the correspondence of the diagrams and the electrocardiograms, as well as their anatomical angles and electrical axes.*

Column A.D.	Column C.D.	Figs.	Observed Values of R Corrected in accordance with Standardization lead I + lead III	Derived Value of R, lead II.	Observed Value of R, lead II.	Ana- tomical Angle.	Electrical Axis
		1	8.90 + (- 0.50)	8.40	8.29	29°	27°
1	1	2	5.71 + (- 0.87) =	4.84	4.84	29	22°
2	9	3	15.35 + (- 11.71) =	3.64	3.81	- 11°	- 16°
3	8	4	7.05 - 1.21	5.84	4.27	- 51°	- 159°
4	7	5	- 2.30 + (- 3.62) =	- 5.92	- 6.36	- 91°	- 111°
5	6	6	1.24 + 0.27 =	1.51	1.51	- 131°	40°
			† 13.68 - (- 3.36)	- 17.04	- 16.23	- 131°	- 139°
6	5	7	1.11 + (- 0.55) =	0.56	0.66	- 171°	0°
			† - 14.85 - 3.56	- 11.29	- 10.93	- 171°	- 163°
7	4	8	8.64 - 3.44	12.08	11.15	149°	47.5°
8	3	9	4.66 - 16.61	11.95	13.29	109°	106°
9	2	10	1.97 + 10.77 =	12.74	13.40	69°	82°

\* Einthoven (W.), Bergansius (F. L.), and Bijtel (J.). "Die gleichzeitige Registrierung elektrischer Erscheinungen mittels zwei oder mehr Galvanometer und ihre Anwendung auf die Elektrokardiographie." *Arch. f. d. ges. Physiol.*, 1916, CLXIV, 167.

† Measurements of the S wave.

a range of 80°, as well as curves substantially normal at +149° and +109° (Figs. 8 and 9). The positions of the leads from which these curves were derived is given in Fig. 11, and the correspondence of the figures with these in Table I. In the course of rotating the leads, the form and sign of the T waves also changed, but there is a difference between their behaviour in this and in the normal individual (hereafter called N.I.). In the normal curves the sign of both R waves and T waves was, as has been said, the same. Here, the signs of the T waves bear no constant relation to those

† The - sign indicates angles below a horizontal line, the + sign angles above it.

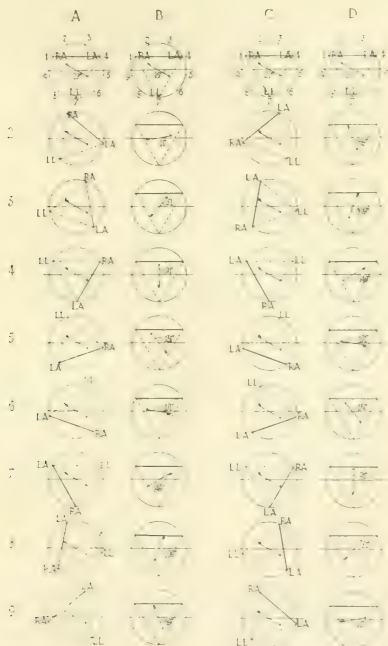


FIG. 11. The columns A, B, and C, D show successive positions of circles containing equilateral triangles. In columns A and C are given the starting points of hearts as the triangle rotates about its centre. In columns B and D the triangles with their contained arrows, shown in columns A and C, are rotated back to the familiar RA-LA positions. The angles given are, in the top row, the actual anatomical angles seen in the roentgenogram in the recumbent position during inspiration; and the theoretical angles obtained under conditions described in the text. In column A the triangles are rotated clockwise; in column C, counter-clockwise. The arrows rotate counter-clockwise in column B and clockwise in column D. Which electrocardiogram was derived from each of these positions is given in Table 1.

of the *R* waves even in those curves (Figs. 2, 3, 4 and 10), which exhibit the forms of left preponderance. If the curves of the left and right preponderance (Figs. 4 and 6) are compared, the form of the *T* waves in lead *I* is the reverse of the *R* waves: in the other leads, especially in lead *III*, an account such as this is incorrect. It is not intended that this description be taken to mean that a profound relation between the two waves does not exist, nor that the alterations found are not due to the position of the leads. It has a different purpose: it is to show that this description of the facts, that is to say, the like signs in *R* waves and *T* waves, found in N.L., is not

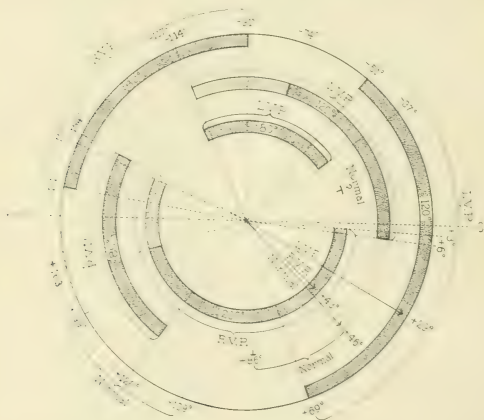


FIG. 12. Segments of the circumference of three concentric circles are shown. On the outer circle are plotted the range and location of left preponderance curves of an individual showing left preponderance in curves derived from chest leads. On the middle circumference are shown similar data taken from curves of a normal individual, presenting a normal electrocardiogram. On the inner circumference are entered similar data obtained from an individual showing curves of right ventricular preponderance. At  $+29^\circ$ ,  $+43^\circ$  and  $+46^\circ$  there are arrows indicating the natural anatomical angles of the heart of the normal individual ( $+46^\circ$ ); of the individual showing curves of left preponderance ( $-29^\circ$ ); and of the individual showing curves of right preponderance ( $+43^\circ$ ).

duplicated in this case, perhaps because the *T* waves in the first place are not so prominently, and, in the second place, not so simply formed.

It is instructive to indicate on the circumference of a circle at which anatomical positions, both normal and artificial curves of right and left ventricular preponderance were obtained, and to compare these results



with those of N.I. previously reported. In L.V.P., curves of left preponderance were found between  $+69^\circ$  and  $-51^\circ$ , a range of  $120^\circ$  (Fig. 12). In the same figure, on a circumference drawn within and concentric with this one, the measurements obtained from the curves of N.I. are given. In him, the signs of left preponderance were found between  $+6^\circ$  and  $-114^\circ$ , a range also of  $120^\circ$ . In L.V.P., the signs of right preponderance appear at angles between  $-91^\circ$  and  $-171^\circ$ , a range of  $80^\circ$ ; in the normal case, between  $-154^\circ$  and  $+126^\circ$ , a range also of  $80^\circ$ . So far as the *Q.R.S.* complexes indicative of preponderance in these two cases are concerned, they cover similar ranges and differ only in respect of the anatomical angles at which

TABLE II.

*Showing the correspondence of the diagrams and the electrocardiograms, as well as their anatomical angles and electrical axes.*

Column A-B.	Column C-D.	Figs.	Observed Values of R Corrected in Accordance with Standardization lead I—lead III		Derived Value of R, lead II.	Observed Value of R, lead II.	Anatomical Angle.	Electrical (°)
		13	0.12 +	8.27 =	8.19	8.68	$43^\circ$	$89^\circ$
1	1	14	0.32 =	10.42 =	10.74	9.91	$43^\circ$	$91.5^\circ$
2	9	15	8.13 + (0.68)		7.45	6.28	$3^\circ$	$26^\circ$
3	8	16	15.18 + (8.87)		6.31	5.53	$-37^\circ$	$-9^\circ$
4	7	17	4.72 +	1.18 =	5.90	5.45	$-77^\circ$	$42^\circ$
5	6	18	0.28 =	0.24 =	0.52	0.57	$-117^\circ$	$55^\circ$
			† - 1.33 + (6.61)		-7.94	-7.45	$-117^\circ$	$-100^\circ$
6	5	19	0.51 =	1.57 =	1.06	1.09	$-157^\circ$	$108.5^\circ$
7	4	20	8.01 +	4.67 =	3.34	3.60	$163^\circ$	$-3^\circ$
8	3	21	6.42 =	8.42 =	2.00	1.47	$123^\circ$	$141^\circ$
9	2	22	- 2.50 =	12.10 =	9.60	9.87	$83^\circ$	$101^\circ$

\* Einthoven (W.), Bergansius (F. L.), and Bijl (J.). "Die gleichzeitige Registrierung elektrischer Erscheinungen mittels zweier oder mehr Galvanometer und ihre Anwendung auf die Elektrokardiographie." *Arch. f. d. ges. Physiol.*, 1916, CLXIV, 167.

† Measurements of the S wave.

they are found, the difference being an advance in a clockwise direction of  $63^\circ$  on the part of the curves of L.V.P.. Normal or approximately normal curves were obtained over a like range in both cases. In both cases also the sharpest change between the right and the left forms took place in  $40^\circ$ .

The curves of the case of right ventricular preponderance (hereafter called R.V.P.) (Fig. 13) are to be contrasted with these. The anatomical angle of this heart was  $43^\circ$ . Curves (Figs. 14-22) were taken at points found by rotating a triangle according to the plan adopted in the other cases. The diagrams indicating their derivations are given in Fig. 23. In Table II

are found the corresponding angles and curves. Curves indicative of right preponderance were found over a range of  $200^\circ$ , from  $+3^\circ$  to  $-157^\circ$  (Figs. 14, 15, 21 and 22). The curves taken at  $-157^\circ$  and  $+163^\circ$  are intermediate in form (Figs. 19 and 20). The curves of left preponderance were found over a range of  $80^\circ$ , from  $-37^\circ$  to  $-117^\circ$  (Figs. 16, 17 and 18). No curve resembling the normal was found. If additional curves had been taken between those obtained at  $+3^\circ$  and  $-37^\circ$  (Figs. 15 and 16), one resembling normal might have been found. For between these positions the *S* waves in lead *I* became shorter, and the *Q* waves in lead *III* became longer. The position at which this curve may have been found is indicated on Fig. 12. If this surmise is correct, the curve resembling normal in this series is to be found, passing in a counter clockwise direction, between the curves showing right and those showing left ventricular preponderance. It is in this situation that the normal curves were found in the other two series. On a third, innermost, circumference (Fig. 12) these values are indicated.

As in the curves of L.V.P., the *T* waves, especially in lead *I* in the curves of the limb leads (Fig. 13) and of the corresponding ones of the chest leads (Fig. 14), have signs opposite to those of the *R* waves. But as the triangle of the leads is rotated the same lack of simple correspondence in the behaviour of the sign of these two waves, *R* and *T*, appears. What was said of this phase of the subject in the discussion of L.V.P. may be repeated here. Compare the curve of right preponderance (Fig. 15) with that of left preponderance (Fig. 16); the *T* waves in leads *I* and *III* have similar, and not opposite, forms. The *T* waves, moreover, in the six curves of right preponderance (Figs. 14, 15, 19 to 22) differ distinctly. To say this is, however, to say no more than, as was stated in discussing similar

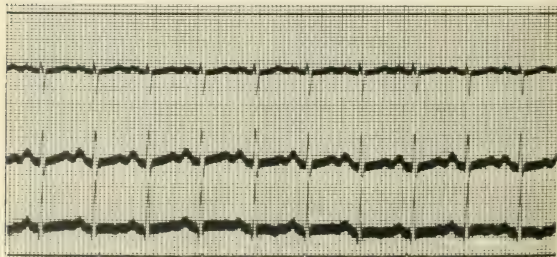


Fig. 13.



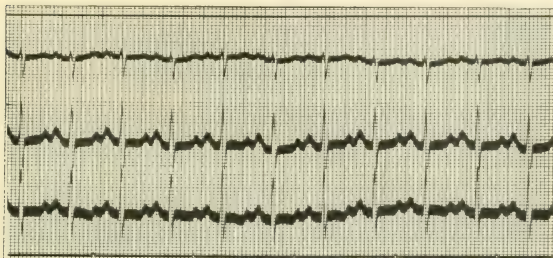


Fig. 14.

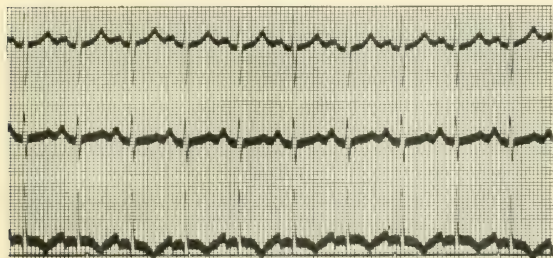


Fig. 15.

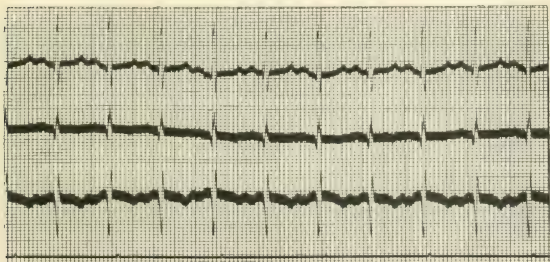


Fig. 16.

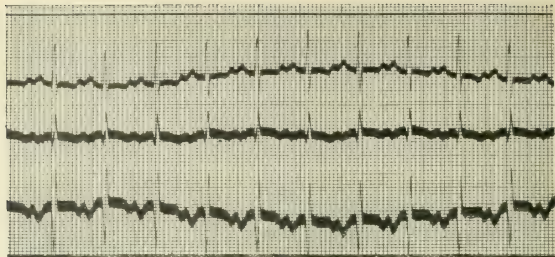


Fig. 17.

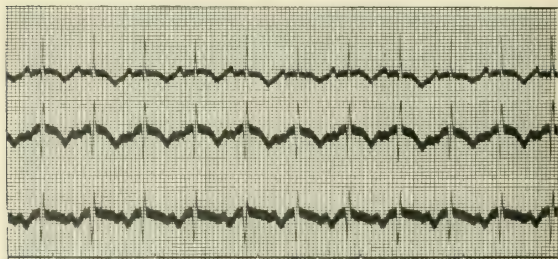


Fig. 18.

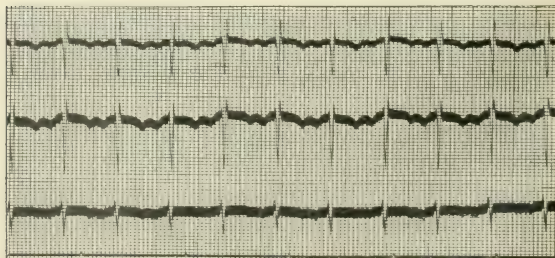


Fig. 19.

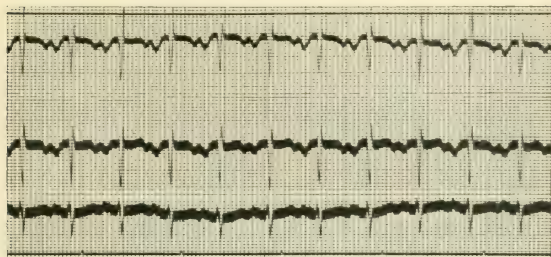


Fig. 20

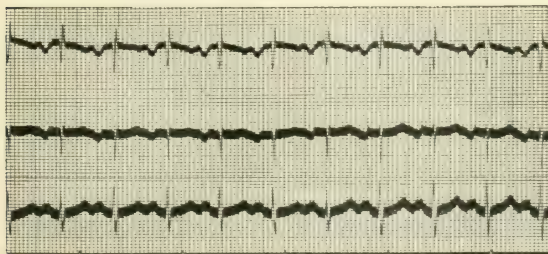


Fig. 21

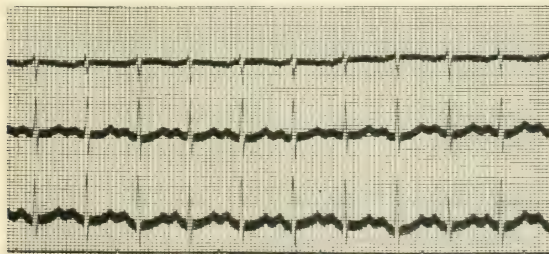


Fig. 22

Figs. 13-22. In each figure curves are presented from electrocardiographic leads, *I*, *II* and *III* from above downward. They are taken synchronously by three galvanometers. The technique of taking them is given in an earlier paper. Divisions of the ordinates equal  $10^{-4}$  volts. Divisions of the abscisse 0.04 of a second. Fig. 13 is of the usual limb leads. In Fig. 23 is given the derivation of each of the other leads. The original curves are sharply

facts in the case of L.V.P., that it is more difficult to make general statements of the behaviour of these more intricate waves in cases of preponderance than was possible in N.I.. Although the data are too limited to permit a general statement, they indicate the existence of a difference in behaviour between the normal heart and the cases of cardiac enlargement. If in the light of greater experience this difference is shown to obtain generally, a new point in the distinction between curves resulting from cardiac enlargement and those due to position alone may be established. The curves at our disposal allow no more than this suggestion.

The differences between the curves of N.I. and L.V.P. on the one hand, and of N.I. and R.V.P. on the other, are shown on comparing the ranges and the positions of the three when these are indicated on concentric circumferences (Fig. 12). Those of L.V.P. and N.I. have already been discussed. When the curves of left preponderance derived from R.V.P. are compared with the others, they are found to cover a much contracted range, that is to say,  $80^\circ$ , from  $-37^\circ$  to  $-117^\circ$ . The transition between right and left preponderance, as in the other cases, takes place sharply in  $40^\circ$ , between  $-37^\circ$  and  $+3^\circ$ . The curves of right preponderance have, on the other hand, a wide range,  $200^\circ$ , wider by far than the range of left preponderance occupied by L.V.P.. No curve approximating normal was obtained. The location of a probable normal point is far removed from the normal points in the other two cases: in them, the curves of approximately normal appearance lie in the lower half of the circle, while that of R.V.P. is found in the upper half. It has already been pointed out that so far as the appearance of left preponderance is concerned, L.V.P. is advanced  $63^\circ$  beyond the normal, in the sense of clockwise rotation. R.V.P., on the contrary, lies  $43^\circ$  beyond the normal in a counter-clockwise direction.

It is at the present time impossible to deduce from these curves alone the significance of the data observed when rotations of this sort are made, or the meaning of the extension or contraction of the ranges at which curves of a given type are found. That in certain respects sets from two cases agree and in others fail to do so, may itself represent a manner of describing a set of curves in terms of standards. At the moment they do not simplify conceptions either of the anatomy or of the electrophysiology of the heart. They do, however, make clear certain matters. First, by means of this technique it has been possible to show that there are enlarged hearts which, placed in certain anatomical angles, would yield normal curves. Second, the range of positions over which preponderance curves are found is not necessarily so great as to exclude the possibility that the same heart, if differently placed, might yield normal curves. If, for example, in L.V.P., the anatomical angle had been slightly greater than  $+69^\circ$ , not an impossible

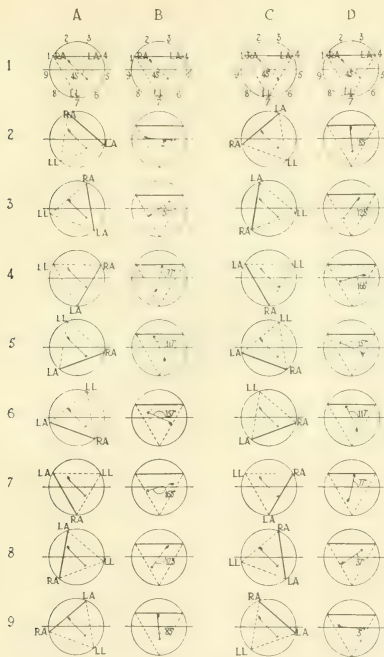


Fig 23

Fig. 23. This figure is similar to Fig. 11, but applies to the case of right ventricular preponderance.

natural angle, enlargement of the heart might have been concealed. It follows from these considerations that:—

1. Curves of preponderance may be derived from normal hearts, as in the case of the soldiers described in our first paper, and the deduction that disease is present may, therefore, improperly be inferred.

2. Hearts which are enlarged and the subject of disease may yield normal curves. The normal curves may similarly be responsible for an incorrect conclusion. There can be no doubt that electrocardiograms when incompletely considered occasion both varieties of faulty conclusion.

3. The form and direction of the *T* wave in the preponderance curves of enlarged hearts do not change in so simple a manner on rotating the leads as was the case in the normal subject investigated. This difference, experience may show, may serve to distinguish true preponderance curves from those dependent for their form on the position of the heart.

4. Two factors at least influence the form of the electrocardiogram, the position of the heart and the type of hypertrophy. The combined influences of these factors determines the positions on the circumference at which the normal and the hypertrophic curves are located.

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## CLUBBED FINGERS AS A SIGN OF SUBACUTE INFECTIVE ENDOCARDITIS.

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(*University College Hospital Medical School.*)

THE clinical observations upon which this report is based were undertaken with the object of enquiring into the relation between clubbed fingers and infection in chronic valvular disease of the heart.

A great deal has been written about clubbed fingers by clinicians in the past. Aristaos of Cappadocia speaks of "the nails of the fingers crooked" in the year 100 B.C.. Caelius Aurelianus<sup>3</sup> later described in some detail this finger deformity, and refers to clubbed fingers as a sign of chronic empyema and of phthisis. Pigeaux<sup>6</sup> in 1832 first uses the expression *hippocratic fingers*. He noted curving of the nails in 167 of 200 phthical patients; he also recorded this sign in many patients emaciated from chronic disease. Pierre Marie,<sup>7</sup> in 1890, reported a case in which, among other signs, clubbing of the fingers was an outstanding feature, and he gave to this condition the name *osteo-arthropathie hypertrophiant pneumonique*. Based on a clinical study of this case, and an analysis of others, he concludes that the lesion is primarily one of the respiratory tract: that here putrefactive substances are produced, which carried into the circulation have a selective action on certain parts of the bones and articulations. A year later Bamberger<sup>1</sup> reported a series of cases with chronic lung or heart disease, and noted that clubbing of the fingers in the heart cases was not associated with bone changes. Certain of these were certainly cases of ulcerative endocarditis: some were diagnosed, others not. He looked upon finger clubbing in congenital heart disease as a sign of venous stasis; but admits that many cases of chronic heart disease present signs of venous engorgement without finger clubbing. He attaches no other particular importance to this sign. Walters<sup>10</sup> in 1895 considers there are four types of clubbed fingers; (1) clubbed fingers with alteration in the long bones as seen in pulmonary osteoarthropathy; (2) clubbed fingers only; (3) a mixed form with primary thickening of the terminal phalanges; (4) clubbed fingers of chronic heart and lung disease. Walters observed clubbing of the fingers

in congenital heart disease; he saw it in foetal life, and noted that there were no bone changes. He records clubbing in a seven-year-old girl with mitral insufficiency; in a patient with specific disease and aortic regurgitation; in a man with angina pectoris he saw this sign develop in a few weeks. Gilbert<sup>5</sup> found finger clubbing in many cases of biliary cirrhosis; he saw it in enterogenous cyanosis. Recklinghausen observed unilateral clubbing associated with aneurism of the right subclavian artery. He states that in one case of subclavian aneurism the clubbing disappeared. Pigeaux considers finger clubbing due to a local circulatory disturbance with a consequent œdematous swelling and heaping up of the nail matrix. He thought that if the nail matrix was raised above the nail bed that the nail must grow downwards towards the palmar surface. Herz,<sup>6</sup> by experimentally widening the capillaries, produced finger clubbing. Kolliker thought that the formation of the nail substance depends upon the vessels of the nail bed; that a frequent changing condition of the nail bed liable to an irregular growth of the nail—a thickening, thinning, or even loss of the nail, and that the deformity in cyanosis and phthisis depends upon this. Esbach<sup>4</sup> asserts that there is increased nourishment with new tissue formation of the nail plate. West<sup>11</sup> does not think that the swelling of the pulp is due to œdema. He looks upon the condition as one of sclerodermatous hypertrophy of the cutaneous and subcutaneous tissue due to a local circulatory disturbance. The X-ray examination of the terminal phalanges was negative in all cases observed by him. The morbid anatomy, according to Shaw,<sup>9</sup> is one of fibrous thickening of the rete mucosa with dilatation of the capillary loops under the nail, enlargement of the interpapillary processes without any other alteration of the skin, and an increase in the connective tissues. He favours the view that the mechano-toxic hypothesis of Bèclère<sup>2</sup> offers an ingenious explanation of the pathogenesis of clubbed fingers. Bèclère considers that venous blood naturally contains substances which provoke changes in the fingers, and that if during its passage through the lungs these substances are not removed from the blood, clubbing results.

From this brief historical survey of the clinical observations and pathological studies, it will be seen that clubbing of the fingers has long been associated with certain clinical conditions, more often with chronic disease of the respiratory tract, but not infrequently with congenital maladies and chronic and acquired disease of the heart. Certain theories have been advanced to explain the mechanism of production of this finger deformity. The consensus of opinion seems to have been that clubbing of the fingers is a sign generally associated with toxic absorption or local venous stasis in respiratory diseases, and with the last factor alone in cardiac disease.

It was in 1917, soon after the Sobraon Military Heart Hospital was opened at Colchester, that clubbed fingers first attracted my interest. At this time many patients with chronic valvular disease of the heart were under observation, and occasionally cases of subacute infective endocarditis



occurred in this group. In several subacute infective endocarditis cases, and in these alone, conspicuous clubbing was noticed. It occurred to me that there might be an association between this sign and infection amongst chronic heart cases, and the possibility of such an association was freely discussed amongst the medical officers of the hospital; in a short while systematic observations were made upon the state of the finger tips in all patients admitted to the hospital suffering from structural disease of the heart. I soon became convinced, as did my fellow medical officers, that clubbing of the fingers and subacute infective endocarditis are more than accidentally associated. Before the Military Heart Hospital closed, experience of this association was widened; and the relation became more clearly apparent, until the sign came to be used by all the medical officers of the hospital as one of the most reliable guides to the presence of subacute infective endocarditis in the classes of patients with which we had to deal. To place the matter upon a more definite footing it was later decided to explore the relation afresh and more fully. It seemed desirable to determine the incidence of clubbed fingers in acquired valvular disease of the heart, and to know the after-histories of patients presenting this sign.

For this purpose I have availed myself of the material of Sir Thomas Lewis's clinic at University College Hospital. All patients admitted as cardiac cases to this clinic and showing signs of acquired structural disease of the heart during a period beginning in September, 1919, and ending in March, 1921, have been examined closely, and for the most part repeatedly, for clubbing of the fingers. The total number of cases of acquired structural disease of the heart under observation during this time has been 798. The patients have been Army pensioners, men in their twenties, thirties and forties for the most part. Included in the 798 cases are 77 without definite signs of valvular disease, but in whom signs of myocardial damage were recognised. The remaining 721 all presented signs either of mitral stenosis or of aortic disease. I purposely exclude from this report cases with signs of congenital valvular disease, being concerned in this report with acquired heart disease only.

To give a general survey of the types of cases examined, Table I is published.\* Of a total number of 798, 341 or 42% presented signs of aortic regurgitation; 219 or 27% those of mitral stenosis; of the remaining 238, 31 had aortic stenosis and regurgitation, 130 aortic disease and mitral stenosis, and 77 no signs of valvular disease. The table is arranged to classify the cases according to etiology, degree of cardiac enlargement, etc.. The figures in brackets represent the number of cases presenting clubbed fingers in each sub-group: 63 or 8% of all the cases showed this sign definitely. The ends of the fingers appear swollen and rounded. The nails are convex and there is an increase in the connective tissue at the base of the nails and

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\* This table is a simplified form of that now in use in the department for purposes of classification.

TABLE I.

	History or Signs of	NO CONGESTION.			CONGESTION.			Total No.
		Much enlarged.	Enlarged.	No signs of enlarge-ment.	Much enlarged.	Enlarged.	No signs of enlarge-ment.	
AORTIC REGURGITATION.	Rheumatic fever	1	2	—	—	—	—	3
	Normal rhythm	9 (2)	48 (3)	5 —	4 (1)	4 (4)	—	70 (13)
	Syphilis	—	13 (1)	—	—	2	—	16 (1)
	Aortic dilatation	20 (1)	26 (1)	2 (1)	—	3 (1)	—	51 (2)
AORTIC STENOSIS and REGURGITATION	Nil	8 (3)	36 (3)	3 —	—	5 (1)	—	55 (4)
	Normal rhythm	27 (2)	96 (8)	10 —	6 (6)	7 (6)	—	146 (42)
	Normal rhythm	1	3	—	1	1	—	6
	Aneurism or aortic dilatation	1	1	—	—	—	—	2
AORTIC DISEASE and MITRAL STENOSIS	Nil	—	1	—	—	—	—	1
	Auricular fibrillation	1	—	—	—	—	—	1
	Normal rhythm	3	18 (1)	—	—	—	—	21 (1)
	Auricular fibrillation	1	—	—	—	—	—	1
AORTIC DISEASE and MITRAL STENOSIS	Normal rhythm	13 —	50 (1)	3 —	—	1	—	67 (1)
	Normal rhythm	2	3	1	—	2	—	8
	Normal rhythm	—	1	—	1	—	—	2
	Auricular fibrillation	—	—	—	—	—	—	—
AORTIC DISEASE and MITRAL STENOSIS	Normal rhythm	—	40 (2)	4 —	5 (3)	2 (2)	1 —	52 (7)
	Normal rhythm	—	—	—	—	—	—	130 (8)

MITRAL STENOSIS	Rheumatic fever	Auricular fibrillation						14 (1)
			—	8	—	3	3	
		Normal rhythm	2	62 (3)	17	1	1	83 (3)
REMAINDER	Nil	Auricular fibrillation	6	11 (1)	2	5	1	28 (1)
		Normal rhythm	4	51 (1)	35	1 (1)	3 (3)	94 (5)
	Rheumatic fever	Auricular fibrillation	1	3	—	—	1	5
		Normal rhythm	—	5	—	—	—	5
	Syphilis	Aneurism	—	3	—	1	—	1
		Aortic dilatation	1	1	—	—	—	2
		Normal rhythm	2	4	—	—	1	7
	Neither	Auricular fibrillation recd	—	—	1	—	—	1
		Auricular fibrillation	—	13	3	1	2 (1)	19 (1)
		Normal rhythm recd	3	5 (1)	—	—	—	8 (1)
		Normal rhythm	3	18	3	1	1	26 77 (2)
	Total		116 (4)	522 (26)	89	35 (14)	41 (19)	798 (63)

on the palmar surface of the finger tips, or a lateral widening of the pulp of the finger. There are not necessarily signs of local venous stasis, giving a redish or cyanosed appearance, as in the clubbed fingers associated with congenital heart disease. The finger tips are in some distinctly pale, in others the colour is in no way different from that of normal healthy skin. In some the changes in the finger tips are associated with hard and scaly hands, frayed nails or nail bed, or other signs of local injury. The clubbed or dumbbell appearance of the ends of the fingers is more striking in some than others, but only those presenting definite finger deformity are included in this report.

Forty-two cases with clubbed fingers had aortic regurgitation, 10 had mitral stenosis, one aortic stenosis and regurgitation, 8 had both aortic disease and mitral stenosis, and there were 2 without signs of valvular disease. The heaviest incidence of clubbing lies clearly in the aortic groups: it is 12% as compared with 4.5% in the mitral stenosis group and 6% in the group with lesions of both valves. 721 cases of the whole series or 90% had no signs of venous engorgement, and of these, 30 or 4% had clubbed fingers: 77 or 10% had definite signs of venous engorgement, and of these, 33 or 43% had clubbed fingers.

The heart was much enlarged in 145 or 18%, and finger clubbing was observed in 18 or 12% of these. Moderate or slight enlargement was noted in 563 or 70%, and signs of clubbing were reported in 45 or 8% of these. The heart was not enlarged in 90 cases, and clubbing was not observed in any of these.

There was a history of rheumatic fever in 254 cases, and 18 or 7% of these had clubbed fingers. 146 either had a history or showed signs of syphilis, and in 7 or 5% the presence of clubbing was noted. In a larger number, 398, there was no history of rheumatic fever nor signs of syphilis; 38 of these or 10% had clubbed fingers.

It is clear from these figures that in acquired chronic valvular disease the incidence of clubbed fingers is relatively highest in those cases presenting signs of venous engorgement; that clubbed fingers is more frequently associated with aortic disease than with mitral disease, and is least often observed when signs of valvular disease are absent; that clubbing is relatively more frequent in those with signs of considerable enlargement than in cases with moderate or slight increase in the size of the heart; and that it is not seen or at least relatively infrequently in cases without signs of cardiac enlargement. It is somewhat more often noted in patients giving a history of rheumatic fever than in those with a history or signs of syphilis. In many cases presenting this sign there is no history of either infection; in fact, the incidence is nearly as high in this group as in the rheumatic and syphilitic groups combined. This analysis reveals two chief associations: the most striking is the relation between clubbed fingers and congestion of the venous system, the less striking the relation between clubbed fingers and aortic disease. Even in the first, however, the relation does not even approach

toward the absolute. The meaning of these relations becomes apparent when it is realised that almost all our cases of subacute infective endocarditis have presented unequivocal signs of venous congestion, and that in the group with infective endocarditis aortic lesions predominate. The relation of clubbed fingers to congestion and aortic disease is not a direct relationship.

*Relation to infective endocarditis.*

Details of the individual cases with clubbed fingers are given in Table II. Here are tabulated for each case the age, the history of rheumatic or syphilitic infection, duration of symptoms, the signs of structural disease of the heart, and the signs of infection. The object of this table is to display the close association of clubbed fingers with infective endocarditis. In *Cases* 1-44 or 70% of the 63 cases analysed, the diagnosis of subacute infective endocarditis was unavoidable. An infective lesion was suspected in *Cases* 45-48, but a diagnosis could not be reached. In *Cases* 49-63 there was no evidence of infection.

*Seventeen cases with post-mortem confirmation of infection.* In *Cases* 1-17 the diagnosis of subacute infective endocarditis rests upon the following signs: chronic valvular disease associated with pallor, splenic enlargement, pyrexia, petechiae and other embolic signs. In one of these pyrexia was absent (*Case* 9), and in two others (*Cases* 2 and 11) embolic signs were not recorded. A post-mortem examination was made in all, and in every case the structural changes found were typical of subacute infective endocarditis.

*Thirteen cases with manifest signs of infection.* *Cases* 18-30 all presented signs of structural disease of the aortic or mitral valves; splenic enlargement was noted in all; in all pallor was striking, and in only four instances (*Cases* 25, 27, 28 and 29) did we fail to note pyrexia. None of those in whom pyrexia was not recorded were admitted to the wards, so that no real opportunity occurred of determining the presence or absence of fever. In one case alone (*Case* 30) petechiae were not recorded; a careful examination for this sign was not made in this case. A recurrent purpuric eruption was observed in five cases (*Cases* 18-22). These hæmorrhagic spots appearing as a crop on the skin, usually of the lower extremities, fade in a few days and may reappear. This sign is striking, and, like the solitary or scattered petechiae, a helpful sign in the diagnosis of subacute infective endocarditis. In *Cases* 18, 20, and 25-30, gross signs of embolic obstruction of a large artery were observed: in *Case* 20 the axillary artery, and in the others the posterior tibial artery was affected. Hæmaturia was noted in *Cases* 18, 19, and 21-25. Osler's nodes are stated to be pathognomonic of subacute infective endocarditis. They were seen in *Cases* 23 and 29. In *Case* 21 the streptococcus viridans was grown from the blood stream.\* All in this group are known to have died within a year from the date of diagnosis of

\* In the great majority of the cases blood cultures were not taken.

TABLE II.

HISTORY.						HEART SIGNS.				
No.	Age	Rh. Fever.	Syph. tils.	Service over-seas.	Duration of Symptoms.	Duration from diagnosis to death.	Venous congestion.	Heart enlarged.	Valves	Clubbed fingers.
1	29			Yes	4½ years	10 months	No	—	Aortic regurg.	—
2	30			..	2½ years	9 weeks	—	—	.. ..	—
3	23			..	5 years	5 months			.. ..	—
4	26			..	4 years	5 weeks		+	.. ..	—
5	27			..	13 12 years	2 months		+	.. ..	+
6	24			..	6 months	6 weeks	—	+	.. ..	+
7	32			..	1½ years	6 weeks	—	+	.. ..	+
8	24		—	..	25 12 years	2 months	—	+	.. ..	+
9	40	—	—	..	18 12 years	3 months		+	.. ..	+
10	45		—	..	9 months	3 months		—	.. ..	—
11	35	—	+	..	3 years	7 months		—	.. ..	—
12	37	—	+	..	3½ months	1½ months		+	Aortic regurg. & mitral stenosis	+
13	27			..	8 months	3½ months	—	—	.. ..	—
14	38			..	2 1/12 years	1½ months		—	.. ..	—
15	40			..	2½ years	1 month			Mitral stenosis	—
16	43	—		..	4 years	5 weeks		—	.. ..	—
17	28			..	1 year	9 months	—	+	.. ..	—
18	36	—		Yes	23 12 years	9 months	—	+	Aortic regurg.	—
19	38	—	—	..	43 12 years	3 months	+	+	.. ..	+
20	23	—	—	..	22 12 years	1¼ months	—	—	.. ..	—
21	36	—	—	..	4 11 12 years	11 months	+	—	.. ..	+

TABLE II.

SIGNS OF INFECTION						
Pallor.	Spleen palpable	Petechiæ.	Signs of emboli.	Pyrexia	Other evidences of infection	Death.
			Hæmaturia. Osler's nodes		<i>P.M.</i> Characteristic vegetations. Splenic infarcts.	From pneumonia. heart failure.
					<i>P.M.</i> Characteristic vegetations. Spleen enlarged with infarcts.	From heart failure.
			Hæmaturia. Embolus femoral artery.		<i>P.M.</i> Characteristic vegetations. Spleen enlarged with infarcts.	From heart failure.
			Hæmaturia.		Streptococci in blood. <i>P.M.</i> Characteristic vegetations. Spleen enlarged with infarcts.	From uræmia.
			Hæmaturia.		<i>P.M.</i> Characteristic vegetations. Spleen enlarged with infarcts. Renal infarcts.	From heart failure.
			Hæmaturia.		Embolus cerebral A. <i>P.M.</i> Characteristic vegetations. Spleen enlarged with infarcts.	From heart failure.
		Recurrent purpura	Hæmaturia.		<i>P.M.</i> Characteristic vegetations. Spleen enlarged with infarcts.	From heart failure.
			Osler's nodes. Post-tibial embolus.		<i>P.M.</i> Characteristic vegetations.	From heart failure.
			Hæmaturia. Osler's nodes.		<i>P.M.</i> Characteristic vegetations. Spleen enlarged with infarcts.	From heart failure.
					<i>P.M.</i> Characteristic vegetations.	From heart failure.
			Osler's nodes.		<i>P.M.</i> Characteristic vegetations. Infarction spleen and kidneys.	From heart failure.
					<i>P.M.</i> Characteristic vegetations. Splenic and renal infarctions.	From heart failure.
		+			<i>P.M.</i> Characteristic vegetations. Infarction of spleen and kidneys.	From heart failure.
			Osler's nodes, embolus of it. brachial.		<i>P.M.</i> Characteristic vegetations. Infarction spleen and kidneys.	From heart failure.
					<i>P.M.</i> Characteristic vegetations. Infarction spleen and kidneys.	From heart failure.
					<i>P.M.</i> Characteristic vegetations. Spleen enlarged. Renal infarction.	From heart failure.
			Hæmaturia		<i>P.M.</i> Characteristic vegetations. Spleen enlarged with infarcts.	From pneumonia.
					<i>P.M.</i> Characteristic vegetations. Infarction spleen and kidneys.	From heart failure.
		Recurrent purpura	Hæmaturia. Post-tibial aneurism.			From heart failure.
			Hæmaturia.			From heart failure.
			Embolus axillary artery.			From heart failure.
			Hæmaturia.			From heart failure.

TABLE II - *continued*.

HISTORY.							HEART SIGNS.			
No.	Age.	Rh. Fever.	Syph. dis.	Service overseas.	Duration of Symptoms.	Duration from diagnosis to death.	Venous congestion.	Heart enlarged.	Valves.	Clubbed fingers.
22	23			Yes	1 1/2 years	5 months		++	Aortic regurg.	
23	39			..	6 months	3 1/2 months	+		.. ..	
24	31			..	1 year	5 1/2 months	+		Aortic regurg. and mitral stenosis	
25	27			..	2 9/12 years	9 1/2 months		++	Aortic regurg.	
26	24	+	-	..	2 years	1 month	-	++	.. ..	+
27	40	-	-	..	1 1/2 years	8 months			Aortic stenosis and regurg.	+
28	26	-	-	..	3 years	3 months	+	+	Mitral stenosis	
29	36	-	-	.	4 years	7 1/2 months	+	+	Aortic regurg.	
30	34		+	..	4 7/12 years	7 months	+	+	.. ..	
31	35			..	3 3/12 years	3 1/2 months		+	.. ..	
32	24	-		..	2 1/2 years	3 months	+	+	.. ..	+
33	35			..	2 years	1 year			.. ..	
34	26			..	2 2/12 years	2 months			Aortic regurg. and mitral stenosis	+
35	33			..	2 5/12 years	5 months	-	++	Aortic regurg.	
36	22			..	2 8/12 years	4 1/2 months		+	.. ..	
37	30			..	2 8/12 years	4 1/2	+		.. ..	
38	37			..	2 years	2 weeks	+		.. ..	+
39	31	+		..	2 1/2 years	1 5/12 years	+	++	.. ..	+
40	28	+		..	2 3/12 years	3 months	+	++	.. ..	+
41	42		+	..	9 months	5 months		+	.. .. (aneurism)	+
42	23	-		..	2 3/12 years	1 month		++	Aortic regurg.	



TABLE II—*continued*.

SIGNS OF INFECTION						Diagnosis.
Fallor.	Spoken palpable.	Petechiae.	Signs of emboli.	Pyrexia.	Other evidences of infection.	
+	+	0	Hematuria.	+		From pneumonia.
			Hematuria.		Streptococcus viridans in blood stream.	From heart failure.
			Osler's nodes.			
			Hematuria.	+		From heart failure.
+	+		Hematuria.			From heart failure.
+	+	+	? Post-tibial embolus.			Died 2 weeks after hemiplegia.
+	+	+	Post-tibial embolus and aneurism.	—		From heart failure.
+	+		Post-tibial embolus.	—		Hemiplegia with death shortly after.
+	+	+	Osler's nodes.	—		From heart failure.
	+		Post-tibial embolus.			
	+		Post-tibial embolus.	+		Death from cerebral embolus.
0	+	+	Osler's nodes.			Hemiplegia with death shortly after.
0	+	—	Osler's nodes.	+		From heart failure.
	+	+	Osler's nodes.	—		From heart failure.
0	+	—	Osler's nodes.	+		From heart failure.
0	+		Hematuria.	+		From pneumonia.
	+	+				Hemiplegia with death shortly after.
+	+	+		—		From heart failure.
	+	+		—		From heart failure.
+		+		—		Hemiplegia with death shortly after.
				+		" "
"		"		+		From acute bronchitis.
0	+	+		—		From heart failure.

TABLE II—*continued.*

HISTORY						HEART SIGNS.				
No.	Age	Rh. Fever	Syph- ms.	Service over- seas.	Duration of Symptoms.	Duration from diagnosis to death.	Venous conges- tion.	Heart en- larged	Valves	Corro- sion of fingers.
43	26	—	—	Yes	3 years	1 year	—	+++	Aortic regurg.	—
44	28	—	—	..	4½ years	15/12 years	—	—	.. ..	—
45	49	+	—	?	14 years	10 months	—	+++	.. ..	+
46	28	—	—	No	5½ years	—	—	—	.. ..	+
47	35	—	—	Yes	34/12 years	5 months	—	—	.. ..	+
48	42	+	—	No	Years	—	—	—	Mitral stenosis	+
49	40	—	—	Yes	4 years	—	—	—	Aortic regurg.	+
50	21	+	—	..	2 years	—	—	—	.. ..	—
51*	30	—	—	..	5½ years	—	—	—	.. .. and mitral stenosis	—
52	31	—	—	..	2 years	—	—	—	Nil	+
53	26	—	—	..	2 years	—	—	—	Aortic regurg.	+
54	35	—	—	..	1½ years	—	—	—	Mitral stenosis	—
55	44	—	—	No	4 years	—	—	—	Nil	+
56	48	—	—	..	20 years	8 months	—	—	Mitral stenosis	+
57	46	—	—	..	4 years	4 days	—	—	Aortic regurg. Mitral stenosis	+
58	37	—	—	Yes	3 years	7 months	—	—	Aortic regurg.	+
59	43	—	—	..	3½ years	3 months	—	—	.. ..	+
60	38	—	—	..	2 years	18 months	—	—	Mitral stenosis	—
61	48	+	—	..	6 years	—	—	—	.. ..	+
62	35	—	—	..	3½ years	—	—	—	.. ..	+
63	39	—	—	..	10 years	—	—	—	Aortic regurg. & Mitral stenosis	+

\* Died from heart failure, an in-patient at U.C.H., in September, 1922, with the diagnosis of subacute infective endocarditis, confirmed at autopsy.

TABLE II—continued.

SIGNS OF INFECTION						Death.
Pallor.	Spleen para- sitic.	Heart cavity.	Signs of emboli.	Dys- rhythm.	Other evidences of infection.	
0	+			-		Hemiplegia with death shortly after.
+	+	+		+		From acute bronchitis.
+	?					From heart failure.
+	?			--		Stationary after 20 months.
0	+	-		-		From heart failure.
+	0	-		--		Stationary after 18 months.
0	+			--		Stationary after 18 months.
0				--		Stationary rejoined army.
0	+		-	-		Stationary after 18 months.
0	+		--	--		Clubbing congenital Stationary after 18 months.
+	0	--		--		Stationary after 18 months.
+	0					Auricular fibrilla- tion developed within a year.
+	0	--	--	--		Stationary after 2 years.
0	0	--	--	--		From auricular fibrillation and heart-failure.
0	0	--	--	--		Sudden death.
0	0		--	--		Hemiplegia and death shortly after.
0	0		--	--		From angina.
0	0		--	-		From heart failure.
0	0		-			Auricular fibrilla- tion after 18 months statry.
0	0		--			Stationary after 22 months.
0	0	--		--		Stationary after 18 months. Clubbing first noted 1888.

subacute infective endocarditis. A post-mortem examination was not possible in any of these, but the clinical evidences of infection are sufficiently distinctive of the disease.

*Fourteen cases with sufficient signs of infection.* In cases 31-44 the signs of infection upon which the diagnosis of subacute infective endocarditis rests are not so complete as in the last group, but in all appeared to us sufficient. Every case showed signs of gross valvular mischief, and splenic enlargement: pallor was absent in six (*Cases* 31, 32, 34, 35, 42 and 43); petechiæ were not seen in five (*Cases* 32, 34, 40, 41, 43), and pyrexia was recorded in only six\* (*Cases* 32, 34, 35, 40, 41, 44). In four, Osler's nodes were observed (*Cases* 31, 32, 33, 34), and in one hæmaturia was noted (*Case* 35). Of five cases (31-35) presenting signs of gross embolism, four showed no pallor (*Cases* 31, 32, 34, 35), in two no petechiæ were observed (*Cases* 32, 34), and no rise of temperature was recorded in two others (*Cases* 31, 33). Although some signs of infection were absent, there was sufficient evidence in these five cases to make the diagnosis certain. No signs of embolism were observed in *Cases* 36-41: there were, however, these signs of infection associated with valvular disease: pallor, enlarged spleen and petechiæ (with two exceptions). In two (*Cases* 40, 41) in whom petechiæ were not seen pyrexia was recorded. There can be little doubt that the signs which these cases presented justified the diagnosis of subacute infective endocarditis.

In *Case* 42 there was aortic disease, splenic enlargement and petechiæ. No mention was made in the out-patient notes of pallor, pyrexia or embolic signs. It is possible one or more of these signs were present, as the patient was only seen on one occasion, and he died at home one month later. It is regrettable that the notes are not more complete: there was, however, no doubt in our minds that the case was one of subacute infective endocarditis. The diagnosis in *Case* 43 was based upon splenic enlargement associated with aortic regurgitation. This patient died a year later in another hospital with the diagnosis of subacute infective endocarditis.

All of these 44 cases are known to have died within a year of the infective condition being recognised. In 17 cases the diagnosis of subacute infective endocarditis was confirmed by autopsy. In 13 other cases the clinical picture was complete and unmistakable. Of the remaining 14 cases, there were 5 with signs pathognomonic of the disease, and 9 with signs which made the diagnosis of subacute infective endocarditis unavoidable.

*Four cases of suspected infection.* The diagnosis of subacute infective endocarditis was suspected in *Cases* 45-48.† There was doubtful enlargement of the spleen in *Cases* 45-46, associated with valvular disease, pallor and

\* The remaining eight cases being observed as out-patients only.

† A number of cases in which subacute infective endocarditis was only suspected on first examination subsequently were recognised as definite cases of the disease and transferred to this group.

petechiae. One of these (*Case 45*) is known to have died ten months after the first examination. The condition of the other, when last heard from, twenty months after the disease was first suspected, was stationary. It is probable that *Case 45* was one of infective endocarditis. The diagnosis in *Case 46* still remains in doubt. *Case 47* died five months after the first examination, out of hospital. The signs of infection were too few to make the diagnosis certain. In *Case 48* infective endocarditis was suspected because of marked pallor associated with mitral stenosis. Eighteen months later the disease had not progressed. With the spleen not enlarged, and no other signs of infection added to those already observed, it is unlikely that this case was one of infective endocarditis.

*Fifteen other cases.* Subacute infective endocarditis was not suspected in *Cases 49-63*. They are included in this table because all presented signs of valvular disease or cardiac enlargement associated with clubbed fingers. *Cases 49-52* had, in addition to clubbed fingers, enlargement of the spleen. No other signs of infection developed within a period of ten to eighteen months, and their general condition has remained stationary. Pallor was associated with clubbed fingers and valvular disease in *Cases 53-55*. The condition of the patient has remained stationary for eighteen months in one, twenty months in the second, and with the onset of auricular fibrillation in the third the disease has progressed with no signs of infection added. In *Cases 56-63* there was clubbed fingers with valvular disease: no other signs of infection were noted in these. Four are known to have died of heart failure, and death followed shortly after the sudden onset of hemiplegia in another. Fibrillation of the auricles developed in *Case 62*, and the finger clubbing was congenital in *Case 63* as in *Case 51*. In all these cases, 49-63, apart from clubbed fingers and the signs already mentioned, no signs of infection were observed within a period of 10-22 months. In none, therefore, was subacute infective endocarditis diagnosed. Clubbing is known to occur in congenital heart disease and in a variety of clinical conditions. Such a deformity can develop during the course of a disease and disappear with the cure of the disease. It is also commonly recognised as a congenital anomaly. Such changes in the finger tips are not infrequently seen in labourers with hard and scaly hands or damaged nails. There may be thickening of the nail bed, and this is not infrequently associated with flaking of the skin about the lunula: a process of chronic superficial irritation is set up, and the tissue changes probably result from this. There are others in whom no signs of local injury can be found: in whom all signs of chronic irritation are absent: in whom there is a complete absence of local or general venous engorgement. The deformity in these may be stated to have been present since birth, or to have made its appearance in early childhood. The deformity is a permanent one, and often it is the physician who first draws the attention of the patient to the condition. *Cases 49-63* belong to this group, and no prognostic significance attaches to the sign in these.

Table III is given to show the relative incidence of death within a period of 22 months of all cases included in these observations. It also displays the relative frequency of signs of infection in the two groups; those with clubbed fingers and those in whom this sign was absent. Within a period of 22 months 51 cases out of a total of 63, or 80%, with clubbed fingers are known to have died. The after-histories of the remaining cases of structural disease of the heart without clubbed fingers show that 27 out of a total of 735, or 3%, died within the same period. It will be seen that signs of infection are rarely observed in the group without clubbed fingers. The spleen was enlarged in 6 cases and pallor was noted in two; no other signs of infection

TABLE III.

	No. of cases.	Club- bing.	Pallor.	Spleen pal- pable.	Pyre- xia.	Signs of emboli.	Py- rexia.	Deaths.	Longest period of observation from diagnosis to death.
Infective endocarditis (post-mortem cases)	17	17	17	17	13	10	16	17	10 months
Infective endocarditis	27	27	22	27	21	18	15+	27	17 "
Suspected infect. endor.	4	4	3	1 (2)	2	0	0	2	10 "
Not suspected of infec- tion	15	15	5	4	0	0	0	5	18 "
Total for clubbed fingers	63	63	45	49	36	28	31	51	
No clubbing .. .. 735		0	2	6	0	0	0	27	22 months

were recorded. The death rate is very high in those with clubbed fingers; 80% as compared with 3% in the group without this sign. Death was due to heart failure in many cases; a cardiorenal death was noted in others. Some died shortly after the onset of hemiplegia. In a few an acute infection of the respiratory tract terminated the disease.

The prognosis in subacute infective endocarditis is known to all clinicians; it is a fatal disease. The diagnosis is by some considered a difficult one in the absence of a bacteriological examination of the blood. It is true that this disease can be, and often is, recognised when the bacteriological report is a negative one. Pallor, pyrexia, and splenic enlargement in chronic valvular disease clearly point to an active infection. Pallor is not always present, the spleen may not always be palpable, and pyrexia is often absent over considerable periods, and is usually absent at the time of examination of out-patients. It has been shown that in patients suffering

from chronic valvular disease the presence of clubbed fingers is usually associated with active vegetations of the subacute or chronic type, and that in consequence of this infection the disease terminates fatally.

### *Summary.*

In 798 cases of structural disease of the heart in pensioners of the recent war clubbing of the fingers was noted in 63 instances.

This group of 63 cases has been subjected to careful and prolonged examination, and the after-histories of the individuals have been followed until death, or for periods in no case less than eighteen months from the date of diagnosis.

Of the 63 cases, 44 cases proved at the time of the first examination or subsequently to be clear instances of subacute infective endocarditis. These cases, without exception, died within seventeen months of the first diagnosis of the infection, and in the 17 where post-mortem examinations were available the original diagnosis was confirmed.

Of the remaining 19 cases, 4 others presented signs of infection which were regarded as doubtful, but not conclusive. Two of the 4 died within a short period and were almost certainly infected cases. The remaining two are still alive and are almost certainly not cases of infective endocarditis.

Of the 15 cases remaining out of the 19 subacute infective endocarditis has in no case been suspected. In two of these 15 the patients stated that their fingers had been clubbed for periods of very many years. In a number of others the clubbing consisted of thickening of the nail bed, and this was associated with small breaks in the skin of the lunula of the nail and a process of chronic superficial irritation. In none of the 15 cases were there physical signs of disease of the lungs. Of the 15 cases, 5 succumbed during the period over which the after-histories of the infected cases were followed.

### CONCLUSIONS.

In cases of structural heart disease occurring amongst adults, clubbing of the fingers is usually associated with subacute infective endocarditis.

Although clubbing of the fingers is not to be regarded in these cases as a conclusive sign of infection, it is nevertheless one of the most valuable signs we possess in coming to a correct diagnosis.

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OBSERVATIONS RELATING TO THE ACTION OF QUINIDINE  
UPON THE DOG'S HEART: THE REFRACTORY PERIOD  
OF, AND CONDUCTION IN, VENTRICULAR MUSCLE.\*

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A CONSIDERABLE amount of experimental work has been already performed, with regard to the action of quinidine, upon the cold-blooded and warm-blooded heart, owing to the interest which has been aroused by the action of this drug in clinical cases of auricular fibrillation. In previous studies in this laboratory,<sup>5</sup> concerned as they were with auricular fibrillation, the action of quinidine upon the mammalian auricle has been so far the chief centre of interest. The main effects of the introduction of quinidine was found to consist in a lengthening of the refractory period, and a depression in the rate of conduction, and these findings of experiment are consistent with observations of clinical cases during quinidine therapy.

The presumption would almost seem justified that similar changes are occurring in other parts of the heart, including the ventricle. It, however, seemed advisable to obtain direct evidence of the effects of quinidine in ventricular muscle, and, when it is appreciated that not infrequently the ventricular rhythm changes during the administration of the drug, this evidence becomes desirable, in order to arrive at an explanation of the mechanism which may underlie these altered rhythms. The following work concerns itself in the main with the two factors mentioned above and was carried out with the intention of obtaining direct measurements of the refractory period and the rate of conduction during quinidine administration, thereby to test the assumptions of previous experimental and clinical work.

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\* Observations undertaken on behalf of the Medical Research Council.

*The refractory period.*

The experiments were carried out along precisely the same lines as those in which auricular muscle was under consideration<sup>3-5</sup>, and the same precautions, which were fully discussed in the communications cited, were adopted in order to arrive at accurate measurements of the refractory period. The ventricles were driven at a constant rate throughout the experiment by rhythmic break shocks passed through fish-hook electrodes embedded in the musculature, and the testing shocks were passed through the same pair of electrodes. The left ventricle was chiefly investigated, as this ventricle, owing to its thicker wall, is more useful for estimations of the rate of conduction; but on one occasion the right ventricle was also tested. In Table I are shown readings from a series of dogs, which are measurements\* of the refractory period before and after the introduction of quinidine; it is divided, for the sake of convenience, into three sections.

Section A deals with unatropinised dogs, in which the vagi had been cut, and in which doses of quinidine,† comparable to those given in previous experiments on auricular muscle, were administered. In all these dogs, after the first injection, a lengthening of the refractory period is evident, which, with further administration of the drug, is progressively increased.

In section B the measurements from two dogs are tabulated. In these dogs two injections of 0.5 of a c.c. of 1 per cent. atropine sulphate solution were given prior to the introduction of quinidine.‡ The lengthening of the refractory period was again obtained in these experiments, and confirms the results of Section A of the Table. In these two sections the lengthening of the refractory period obtained is of the same order as that which has been found for auricular muscle, namely, 50-100 per cent.. In Section C, readings from two further dogs are shown. In these experiments, however, the quinidine was administered in a series of small doses over a considerable period of time. Consequently the same degree of change is not to be expected: the lengthening of the refractory period should be of smaller degree, and is complicated by the elimination of the drug which proceeds *pari passu* with the administration.

In both dogs a small initial lengthening of refractory period was seen: this lengthening in dog PX remained unchanged, or diminished, till at 3.10 p.m. the refractory period was at its original value, but rose again upon further administration of quinidine. In this case, the rate of the natural heart beat was taken throughout the experiment, and it was seen that at 3.10 p.m. recovery was taking place, and this fact, associated with the

\* Responses always occurred when the intervals were greater than the largest, and never occurred when the intervals were less than the smallest values shown in the Table.

† 0.1 grm. of quinidine sulphate was dissolved in 20 c.c. of salt solution and injected slowly into the femoral vein.

‡ The action of atropine sulphate upon the factors under consideration is under investigation.

time which had elapsed since the control readings were obtained, is sufficient to explain the unusual values obtained in this dog.

In all these experiments care has been taken to ensure that the testing shocks were of sufficient strength to give a measurement which represents the absolute refractory period of the ventricles: for this purpose break shocks have for the most part been used of a strength 10-12 times, at least, above the threshold value. Such an increase in strength is sufficient to ensure a measurement which represents, with a negligible error, the absolute refractory period of muscle. Furthermore, in those tables in which break shocks are alone tabulated, the refractory periods were also calculated from make shocks, and, in this series, the value of the refractory period remained unchanged. The make shocks were about 2-6 times weaker than the break shocks. This is in support of the readings being true measures of the absolute refractory period. When, as in some experiments, the results of using make shocks have been introduced into the tables, owing to a scarcity of observations, only those which elicited responses have been employed. These are marked by the letter *M* in Table I. The table shows clearly that the refractory period of the ventricle is lengthened by the administration of quinidine.

Chief stress is laid upon the figures which are obtained after the initial doses of quinidine sulphate: the figures obtained after subsequent injections are confirmatory of the earlier readings.

The initial doses only are likely to give rise to conditions in the heart which are comparable to those produced during quinidine therapy: in the later stages of the experiment and on repeated dosage changes in the threshold excitability are often so great as to interfere with accurate measurements of the refractory period.

This criticism applies especially to those stages of experiment in which a 1:1 2:1 response of the ventricle occurs with rhythmic shocks: the threshold excitability is changing rapidly, and as the strength of shocks is raised, in order to test if the 1:1 2:1 response is brought about by a much lengthened refractory period, or to a markedly depressed excitability, ventricular fibrillation sets in, and ends the observations. In some experiments, however (dog PP of this series), ventricular fibrillation did not occur, and the excitability falls away so completely that it becomes inexcitable to rhythmic induction shocks, though these were used many times above the original threshold value. This change of excitability in later stages makes it difficult to conclude if prolonged refractory period alone or loss of excitability is the cause of the 1:1 and 2:1 responses. The earlier figures, however, remain undisturbed, as there is no appreciable change in excitability at first: the period under discussion develops with great rapidity, and complete inexcitability is reached in the space of a few moments, or ventricular fibrillation sets in.

TABLE I.  
*Influence of quinidine sulphate upon refractory period.*  
 SIXTEEN A. 4 unresponsive dogs. Vag sectioned.

Dog P†			Dog P‡			Dog P§		
Quinidine Soluph. 0.10 gm. at 12.25 p.m.	Quinidine Soluph. 0.10 gm. at 1.00 p.m.	Quinidine Soluph. 0.10 gm. at 1.25 p.m.	Quinidine Soluph. 0.10 gm. at 1.30 p.m.	Quinidine Soluph. 0.10 gm. at 1.35 p.m.	Quinidine Soluph. 0.10 gm. at 1.55 p.m.	Quinidine Soluph. 0.10 gm. at 1.45 a.m.	Quinidine Soluph. 0.10 gm. at 12.42 p.m.	Quinidine Soluph. 0.10 gm. at 12.42 p.m.
Control.	Control.	Control.	Control.	Control.	Control.	Control.	Control.	Control.
R.P. 11.40. 11.50 a.m. (Threshold 7-9 cm. Rate 136.)	R.P. 12.35. 12.41 p.m. (Threshold 7-5 cm. Rate 136.)	R.P. 12.54. 1.01 p.m. (Threshold 7-0 cm. Rate 136.)	R.P. 1.14. 1.20 p.m. (Threshold 6-5 cm. Rate 136.)	R.P. 1.13. 1.50 a.m. (Threshold 9-3 cm. Rate 210.)	R.P. 1.42. 1.52 p.m. (Threshold 9-4 cm. Rate 210.)	R.P. 1.59. 2.05 p.m. (Threshold 8-5 cm. Rate 210.)	R.P. 11.40. 11.45 a.m. (Threshold 10-0 cm. Rate 174.)	R.P. 12.30. 12.42 p.m. (Threshold 7-0 cm. Rate 174.)
0.330	0.358	0.306	0.312	0.214	0.226	0.274	0.218	0.295
0.256	0.356	0.299	0.337	0.191	0.220	0.230	0.216	0.287 M
0.253	0.352	0.298	0.312	0.188	0.218	0.209	0.212	0.280 M
0.242	0.346	0.296	0.304	0.178	0.217	0.185	0.208	0.258 M
0.213	0.340	0.294	0.298	0.174	0.191	0.176	0.204	0.254
0.192	0.337	0.293	0.294	0.172	0.165	0.172	0.185	0.254
0.189	0.322	0.291	0.286	0.163	0.188	0.174	0.176	0.251 M
0.182	0.312	0.288	0.280	0.161	0.186	0.163	0.163	0.251 M
0.177	0.294	0.284	0.274	0.160	0.174	0.156	0.163	0.238 M
0.175	0.282	0.279	0.266	0.155	0.169	0.173	0.156	0.223
	0.283	0.278	0.256	0.149	0.166	0.162	0.150	0.214
	0.282	0.272	0.294	0.139	0.165	0.144	0.150	0.180
	0.281	0.246	0.286	0.132	0.163	0.129	0.145	0.170
	0.244	0.236	0.280	0.130	0.143	0.073	0.142	0.156
	0.246		0.274	0.117	0.139		0.135	0.152
			0.266	0.114	0.134		0.128	0.137
				0.092	0.124		0.115	0.115
							0.084	0.090
0.164	0.228	0.219	0.252					
0.152	0.213	0.211	0.250					
0.137	0.209	0.210	0.244					
0.135	0.197	0.208	0.230					
0.130	0.184	0.186	0.232					
	0.193	0.168	0.227					
	0.165	0.142	0.224					
	0.163	0.139	0.222					
	0.157	0.134	0.219					
	0.153	0.127	0.216					
	0.150	0.123	0.213					
	0.138	0.122	0.210					
	0.117	0.117	0.207					
	0.116	0.116	0.206					
	0.105	0.095	0.205					

Onset of  
ventricular  
fibrillation  
at 12.42 p.m.

Onset of  
ventricular  
fibrillation  
at 2.05 p.m.

Dog died at  
1.37 p.m.

‡The excita-  
bility shortly  
after injection  
began to fall  
away rapidly  
and at 1.33  
although the  
coil was used  
at 0 the ven-  
tricle was ir-  
responsive to  
the rhythmic  
shocks.

SECTION B. *Atropinised dogs.*

<i>Dog 18.</i>		<i>Dog 17.</i>	
<i>Control.</i>	Quinine Sulph. 0.05 g.m. at 2.52 p.m.	<i>Control.</i>	Quinine Sulph. 0.05 g.m. at 1.05 p.m.
Atropine† 0.5 c.c. at 2.18 p.m.		Atropine† 0.5 c.c. at 12.32 p.m.	
Atropine† 0.5 c.c. at 2.33 p.m.		Atropine† 0.5 c.c. at 12.47 p.m.	
R.P. 2.35-2.45 p.m. (Threshold 8 cm. Rate 210.)	R.P. 2.57-3.02 p.m. (Threshold 8 cm. Rate 210.)	R.P. 12.50-1.00 p.m. (Threshold 4.3 cm. Rate 210.)	R.P. 1.08-1.10 p.m. (Threshold 1 cm. Rate 210.)
0.244	0.288	0.198	1:1:2:1 response, Cycle=0.286
0.240	0.288	0.182	
0.238	0.286	0.180	
0.228	0.284	0.178	
0.224	0.284	0.177	
0.215	0.280	0.176	
0.204	0.248	0.171	
0.201	0.245	0.167	
		0.161	
0.184	0.238	0.153	
0.175	0.236	0.152	
0.174	0.235	0.146	
0.162	0.233	0.140	
0.162	0.229	0.137	
0.157	0.229	0.137	
0.150	0.224	0.135	
0.141	0.224	0.128	
0.139	0.224	0.120	
0.136	0.222	0.117	
0.133		0.117	
0.132			
0.123			
0.121			
0.120			
0.113			
			Ventricular fibrillation at 1.12 p.m.

\* Dog 17, right ventricle, remainder, left ventricle tested.

† Atropine = 1 per cent. solution of atropine sulphate.

SHEPHERD C. Untrapped sheep. Vagi sectioned. Quindine given in small doses.

Dog PK.

Dog PK.<sup>2</sup>

Dog PK. <sup>2</sup>		Dog PK.	
Control.	Quindine Sulph. 0.05 gm. given in five separate doses of 0.01 gm. at 1.30, 1.45, 1.57, 12.50, 1.05, 1.09, and 1.15 p.m.	Quindine Sulph. 0.02 gm. given in five separate doses of 0.01 gm. at 1.30, 1.40, 1.50, 1.59, and 1.40 p.m.	Quindine Sulph. 0.02 gm. given in five separate doses of 0.01 gm. at 1.53 and 2.00 p.m.
R.P. 12.25- 12.34 p.m. (Threshold 0.003 amp. Rate 210.)	R.P. 1.21- 1.27 p.m. (Threshold 0.003 amp. Rate 210.) 0.157 0.172 0.166 0.164 0.159 0.158 0.151 0.174 0.159 0.159 0.148 0.135 0.131 0.120	R.P. 1.45- 1.50 p.m. (Threshold 0.0015 amp. Rate 234.)	R.P. 2.05- 2.10 p.m. (Threshold 0.0015 amp. Rate 234.)
0.210 0.174 0.159 0.159 0.148 0.135 0.131 0.120	12.40 p.m. (Threshold 0.0015 amp. Rate 234.)	0.202 0.191 0.182 0.168 0.155 0.154 0.154 0.153	0.199 0.193 0.182 0.179 0.173 0.167 0.161 0.157 0.156
	Natural heart rate 200.	Natural heart rate 180.	Natural heart rate 160.
0.119 0.117 0.115 0.113 0.112 0.100 0.096 0.093 0.088 0.084	0.130 0.117 0.113 0.099 0.098 0.092 0.092 0.087 0.085 0.069	0.152 0.148 0.145 0.137 0.123 0.118 0.116 0.115	0.140 0.131 0.137 0.124 0.123 0.118 0.114 0.109
	Natural heart rate 152.	Natural heart rate 140.	Natural heart rate 122.
	Ventricular fibrillation at 1.28 p.m. after 3 further doses of 0.01 gm. quindine sulphate.	0.138 0.137 0.134 0.118 0.115 0.114 0.111 0.101	0.125 0.121 0.112 0.111 0.103 0.101 0.101 0.101
	Natural heart rate 150. Ventricular fibrillation obtained with difficulty, at 3.47 p.m.		

\* In these experiments the threshold value of the shocks is expressed, not in terms of the distance of secondary from primary coil, but in terms of the current flowing through the primary coil; this was varied, while the secondary coil was not moved.

*Conduction.*

The measurement of conduction has been attempted only in the left ventricle. The method of placing two paired non-polarisable electrodes upon the muscle in line with the stimulating electrodes and reading the time of the arrival of the excitation wave at proximal and distal electrodes, with the ventricle responding at a constant rate to rhythmic shocks, was adopted. In order to avoid early spread through the Purkinje network and the arrival of the forced excitation waves by this channel at either of the pairs of electrodes, the distance separating the stimulating electrode from the distal non-polarisable electrode has been kept small, and the two pairs of contacts have been maintained close to each other. If the thickness of the left ventricle muscle is 10 cms., an excitation wave started in the outer surface from the stimulating electrode must travel through 10 cms. of muscle, along the Purkinje network, and out again through 10 cms. of muscle in order to reach the distal electrode. If the distance separating the stimulating and distal non-polarisable electrode is therefore kept well under 20 cms., a measurement of muscle conduction is obtained.

In Table II a series of measurements obtained from six dogs is shown. Four were unatropinised and the vagi cut, and two were atropinised. In all the animals, a slower conduction rate was obtained after quinidine had been administered, and is most clearly instanced in dogs PU and PX. In these dogs the drug was injected in a series of small doses over a considerable period of time. This method was adopted because it was found that larger doses of the drug introduced conspicuous changes in the forms of the electric responses, often rendering them incomparable as a series. When smaller doses are used this difficulty is avoided. When the form of electric response alters on heavier dosage, the alteration is often associated with a distinct fall in the transmission intervals, suggesting that the same factors as were discussed in previous articles<sup>3, 4</sup> are in play; namely, swerve of the excitation wave, so that it no longer flows in a direct line over the contacts. In the dogs PU and PX a progressive rise in the transmission time is recorded: in the latter dog the value amounts to 150 per cent. above the control. In the dog PU the experiment is divided into two sections, as between 1.04 p.m. and 1.08 p.m., a considerable change in the character of electric response occurred, which, though it prevents an accurate comparison of the intervals in the whole series of observations, does not hinder the compilation of two separate series of comparable readings. The rise which is obtained in these two dogs is displayed in the remainder of the dogs tabulated, in which larger doses of quinidine were given. In the atropinised dogs, there is evidence that atropine itself slows conduction in ventricular muscle,\* so that some degree of impaired conduction is present before the introduction of the quinidine.

\* Under investigation.

TABLE II.—*Influence of quinidine upon conduction in ventricular muscle.*  
(Transmission intervals are given in decimal points of a second.)

<i>Dog PX.</i> (Unatropinised, vagi cut.) Rate 234. Electrodes apart 5-6 mm.	<i>Dog PU.</i> (Unatropinised, vagi cut.) Rate 210. Electrodes apart 8 mm.	<i>Dog PR.</i> (Unatropinised, vagi cut.) Rate 175. Electrodes apart 13 mm.
12.50 p.m. 0-0163.	12.28 p.m. 0-0363.	12.25 p.m. 0-0342.
1.00 " Quinidine 0-01 grm.	12.31 " 0-0357.	12.26 " 0-0330.
1.04 " 0-0161.	12.35 " Quinidine 0-01 grm.	12.27 " Quinidine 0-10 grm.
1.00 " 0-0216.	12.40 " 0-0398.	12.36 " 0-0563.
1.10 " Quinidine 0-01 grm.	12.45 " 0-0393.	12.42 " Ventricular fibrillation.
1.44 " 0-0205.	12.47 " Quinidine 0-01 grm.	
1.19 " 0-0209.	12.52 " 0-0422.	
1.20 " Quinidine 0-01 grm.	12.57 " 0-0348.	
1.24 " 0-0188.	12.59 " Quinidine 0-01 grm.	
1.29 " 0-0267.	1.04 " 0-0409.	
1.30 " Quinidine 0-01 grm.	1.05 " Quinidine 0-01 grm.	
1.34 " 0-0289.		
1.39 " 0-0297.	12.35 to 1.05 p.m. Quinidine 0-04 grm. in 4 separate doses.	<i>Dog PN.</i> (Unatropinised, vagi cut.) Rate 245. Electrodes apart 4-5 mm.
1.40 " Quinidine 0-01 grm.		
1.44 " 0-0297.		
1.51 " 0-0287.	1.08 p.m. 0-0262.	
1.53 " Quinidine 0-01 grm.	1.09 " Quinidine 0-01 grm.	12.36 p.m. 0-0073.
1.56 " 0-0274.	1.12 " 0-0304.	12.37 " Quinidine 0-01 grm.
1.59 " 0-0320.	1.14 " 0-0269.	12.40 " 0-0207.
2.00 " Quinidine 0-01 grm.	1.15 " Quinidine 0-01 grm.	12.42 " Ventricular fibrillation.
2.04 " 0-0312.	1.20 " 0-0281.	
2.11 " 0-0258.	1.28 " 0-0292.	
2.12 " Quinidine 0-01 grm.	1.30 " Quinidine 0-01 grm.	
2.16 " 0-0301.	1.33 " 0-0354.	
2.20 " 0-0317.	1.38 " Ventricular fibrillation.	
2.21 " Quinidine 0-01 grm.		<i>Dog PS.</i> (Atropinised.) Rate 210. Electrodes apart 6 mm.
2.25 " 0-0329.		
2.30 " 0-0329.		
2.31 " Quinidine 0-01 grm.		
2.34 " 0-0335.		
2.40 " 0-0310.		2.18 p.m. 0-5 c.c. atropine.
2.43 " Quinidine 0-02 grm.		2.33 " 0-5 c.c. atropine.
2.47 " 0-0352.		2.45 " 0-0100.
2.52 " 0-0330.		2.47 " 0-0090.
2.53 " Quinidine 0-02 grm.		2.52 " Quinidine 0-05 grm.
2.57 " 0-0356.		2.56 " Intraventricular block.
3.00 " 0-0324.		3.04 " Intraventricular block.
3.01 " Quinidine 0-02 grm.		3.12 " Ventricular fibrillation.
3.03 " 0-0379.		
3.04 " Quinidine 0-02 grm.		
3.07 " 0-0374.		
3.12 " 0-0352.		
3.14 " Quinidine 0-04 grm.		
3.16 " 0-0406.		
3.18 " Quinidine 0-03 grm.		
3.20 " 0-0408.		
3.22 " 0-0394.		
3.23 " 0-0428.		
3.24 " Quinidine 0-03 grm.		<i>Dog PT.</i> (Atropinised.) Rate 210. Electrodes apart 6 mm.
3.25 " 0-0443.		
3.27 " 0-0399.		
3.28 " Quinidine 0-03 grm.		12.32 p.m. 0-5 c.c. atropine.
3.29 " 0-0422.		12.47 " 0-5 c.c. atropine.
3.30 " 0-0308.		12.49 " 0-0376.
3.31 " Quinidine 0-03 grm.		1.00 " 0-0426.
3.32 " 0-0395.		1.05 " Quinidine 0-05 grm.
3.37 " 0-0223.		1.07 " 0-0506.
3.47 " Short runs of ventricular fibrillation, ceasing periodically and ventricular rhythm returning, finally lasting ventricular fibrillation obtained by application of rhythmic shocks.		1.12 " Ventricular fibrillation.

The distance from the stimulating electrode to the proximal non-polarisable electrode was in all cases about 2 mm.



*Excitability of ventricular muscle during quinidine administration.*

Observations have been made throughout upon the excitability of ventricular muscle, before and during the administration of quinidine. The method used was to find the threshold value for a series of rhythmic break shocks of the same rate as that used for testing the refractory period. The method is obviously crude, but serves as a rough guide to changes occurring during an experiment. Very slight changes occur in the excitability measured in this way, till several large doses of quinidine have been injected.\* (The threshold values are tabulated in Table I.) A stage is sooner or later reached, however, when the excitability falls rapidly, and as the strength of the shocks is raised to meet this new condition, ventricular fibrillation usually sets in or the muscle becomes completely inexcitable.

*The onset of ventricular fibrillation.*

The most common termination of these experiments in which quinidine was injected has been ventricular fibrillation. The onset appears to be similar in all cases; when the stage of lengthened refractory period, impaired conduction and falling excitability is reached, a series of almost regular beats arise in the ventricle which bear no relation to the rhythmic shocks. Such beats may be set up in response to a single testing shock during rhythmic stimulation or by rhythmic shocks alone. When these spontaneous rhythms appear the form of the electric responses obtained by direct leads on the ventricular muscle also changes: the usual form with its sharp rise and fall is replaced by a curve in which the string movements are more continuous and in which isoelectric periods are but brief or are absent. Such a series of responses may end, and the ventricle again respond to rhythmic shocks, and a similar series be produced again later. Usually, however, such a series, when once started, holds for a very short while, and gives place to lasting ventricular fibrillation. The phenomena appears very similar to that obtained by Mines in the perfused rabbit's heart<sup>6</sup> and by De Boer in the bleb frog's heart.<sup>1</sup>

This onset of ventricular fibrillation under quinidine is seemingly at variance with the findings of other authors upon cats,<sup>2</sup> and with our earlier observations when, under quinidine, the dog's ventricle has been faradised. It has then been the rule, to which, however, we have seen exceptions, that the ventricle has been thrown into fibrillation with difficulty or not at all. These experiments, however, differ from those which have been described in this paper in that in the latter the ventricle was not tested with a faradic but with relatively slow rhythmic shocks accompanied or unaccompanied by occasional make and break shocks. It seems possible that the method used to elicit fibrillation may materially affect the result: probably, however,

\* Results which are very comparable to those found in auricular muscle.

the explanation of the different reactions is chiefly to be found in the degree of poisoning produced by the drug, the stage in which fibrillation is readily provoked being that in which poisoning is relatively slight, while in later stages and under heavy doses the fall in the threshold of excitability is so conspicuous that the muscle reacts only occasionally to stimulation, or fails altogether. In the earlier experiments referred to the susceptibility of the dog's ventricle to a faradic current was tested only in the very late stages of the experiment.

#### SUMMARY.

Quinidine sulphate given intravenously to dogs, in doses comparable to those used clinically, has the following effects upon ventricular muscle:—

(a) It lengthens the absolute refractory period.

(b) It reduces the rate of conduction.

In the relatively early stages of poisoning the ventricle appears to be in a susceptible condition: passing into rapid spontaneous beating and readily fibrillating in response to relatively slow rhythmic shocks accompanied or unaccompanied by occasional testing shocks.

At a later stage of poisoning a rise in the threshold of excitability to rhythmic shocks is conspicuous and is added to the other effects. At this stage a reduced rate of conduction is, however, difficult accurately to measure. It is chiefly displayed in the altered and often varying forms of the electrical responses which indicate changes in the path followed by the excitation waves.

[The dogs used in these experiments were anaesthetised fully and throughout with morphia and chlorotone, and if necessary, a sufficiency of ether.]

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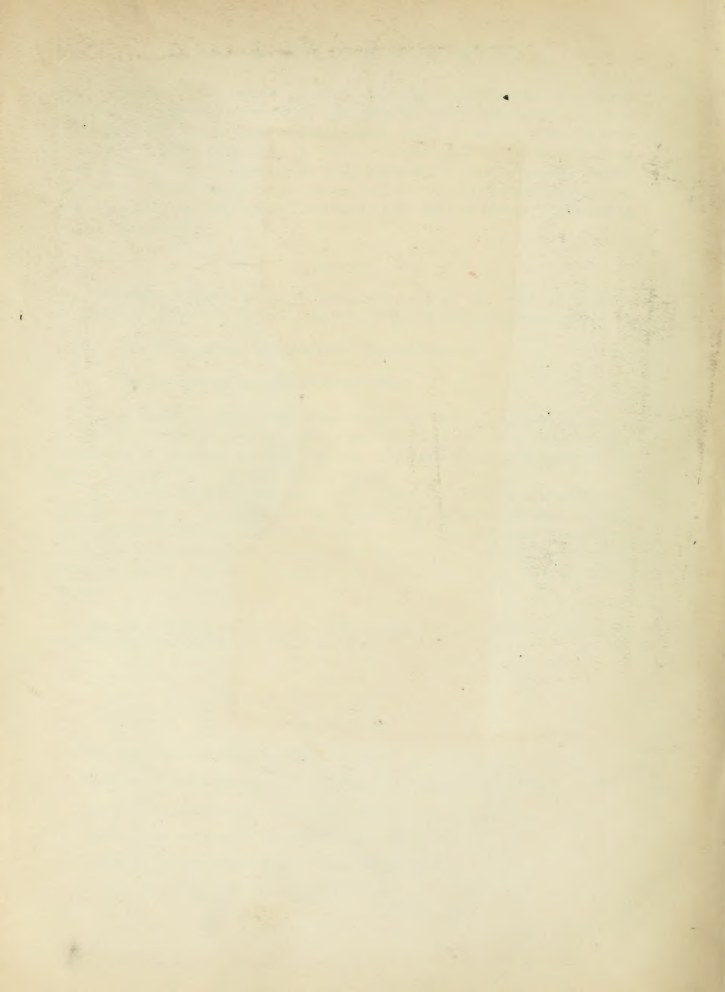
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